RISK FACTORS IMPACTING COLON AND/OR COLORECTAL CANCER MORTALITY AMONG AMERICAN INDIANS/NATIVE AMERICANS AND NON-HISPANIC WHITES

by

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ABSTRACT

Risk factors for colon (or colorectal) cancer mortality for American Indians/Alaska Natives (AI/AN) has been understudied. This project's overall aim is to determine colon and colorectal cancer risk factors among AI/AN. Colorectal cancer risk factors from the literature were determined utilizing systematic review methods. Comorbidities, travel times to screening and treatment, were also explored as risk factors for colon cancer mortality using cox proportional hazards modeling to determine hazard ratios. The systematic review revealed that race was the only risk factor explored for colon or colorectal cancer among AI/AN, whereas numerous colon or colorectal cancer risk factors have been explored for Non-Hispanic Whites (NHW). Next was examining risk for colon cancer mortality by building models. An increasing Charlson comorbidity index had higher risk for mortality among NHW. Models examining travel times that were race specific resulted in greater risk for AI/AN and mortality for those having to travel longer to a chemotherapy facility. Longer travel time to a screening facility increased NHW risk for mortality. NWH increased travel time to a surgical center had a decreased risk for mortality. The regional and distant stage model showed that AI/AN living a distance from chemotherapy had increased risk for mortality. For NHW, living a distance from a screening facility had increased mortality. The all stage model for NHW showed that living further to a screening facility increased mortality risk but living further from a surgical center decreased one's risk for mortality.

For Launce and my father.

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CHAPTER 1

INRODUCTION

There is little known about colon cancer survivorship among American Indians/Alaska Natives (AI/AN). More specifically, risk factors that inhibit survival are largely unknown in the AI/AN population. Less is known about how travel to treatment and screening impacts colon cancer survival among AI/AN and NHW. In order to develop effective programs to improve survival, the area of colon cancer survivorship must be explored to a fuller extent.

Colorectal Cancer Survival Among AI/AN compared to Whites/NHW

Many of the studies focus on colorectal cancer rather than only colon cancer. Colorectal cancer (CRC) survival among AI/AN has been examined for various regions of the United States but on a limited basis. Past studies have found that CRC survival among AI/AN is lower than Whites/NHW in a number of SEER locations.[1-3] During the time period of 1975-1987, Clegg reported that White men (50.5%) and women (49.0%) had a greater probability of survival than AI/AN males (37.9%) and females (41.5%).[1] Similar results were found during the 1988-1997 time period, White males (59.1%) and females (59.7%) had higher survival than AI/AN males (58.0%) and females (46.1%).[1]

Jemal, *et al.* also found similar results in terms of improved outcomes for Whites/NHW than AI/AN. The survival difference for White men was 1.7% and White

women, 5.3%, for the 1992-2000 time period. White men (64.0%) and women (63.4%) had higher survival than AI/AN men (62.3%) and women (58.2%).[2] The Swan, *et al.* study, results were presented in a graph that demonstrated higher survival for NHW than AI/AN for the time period 1988-1997.[3]

In comparison to NHW, AI/AN colorectal cancer survival was lower in Arizona/New Mexico and Western Washington State.[4,5] The Arizona/New Mexico data demonstrated higher 5-year survival for Whites (53.1%) than AI/AN (38.0%), which is a 15.1% difference.[4] As for Western Washington State data, there was a 7.6% survival difference, Whites/NHW (47.3%) having a higher probability of survival after diagnosis than AI/AN (39.7%).[5]

Temporal analysis of survival has been improving for AI/AN but there is still a lag in survival; poorer outcomes among AI/AN persist across time periods with differences being more apparent among women than the men.[1]

Past studies varied in terms of statistical significance when examining whether AI/AN had increased risk for all-cause, colon, or colorectal cancer mortality.[1,2,5,6] AI/AN showed an increased risk for all-cause and CRC mortality, but these findings were not significant.[5,6] Two additional studies found increased risk for CRC cancer mortality among female AI/AN than female NHW.[1,2] Risk for cancer survival may be inconclusive, but when examining life expectancy, rates per 100,000 are lower for American Indians/Alaska Natives (73.6) than Whites (77.7).[7]

Stage at Diagnosis among AI/AN and Whites/NHW

A major factor that affects survival is stage of disease at diagnosis and AI/AN are being diagnosed at later stages.[1,2] One study compared two time periods (1975-1987 and

1988-1997) and found that AI/AN were diagnosed less at the localized stages for the latter time period. The study also found that AI/AN were diagnosed more frequently at regional stages than Whites. During 1975-1987, Whites (34.5%) were more likely to be diagnosed for localized stages than AI/AN (27.2%) and for 1988-1997, 37.6% of Whites were diagnosed at localized stages than 30.1% of AI/AN. For the 1975-1987 time period, there were more Whites (20.3%) than AI/AN (19.8%) being diagnosed for distal stages for colorectal cancer, but for 1988-1997, less Whites (19.5%) were diagnosed for distal stage colorectal cancer than AI/AN (24.4%).[1] Another study found stage at diagnosis rates as more unfavorable for localized diagnosis for AI/AN than Whites for the 1996-2000 time period.[8]

A more recent study has found that there are fewer AI/AN being diagnosed at localized stages and being diagnosed at later stages for colorectal cancer than NHW across various regions in the United States.[9] Accounting for stage and age at diagnosis, survival outcomes are still poorer among AI/AN than Whites.[1-3,5] These past studies have accounted for age, tumor stage, and late stage diagnosis but demonstrate that survival is still an issue for AI/AN. Factors, which affect survival among AI/AN, are still unexplained.

Colorectal Cancer and Public Health

Cancer in general is a public health concern for the AI/AN population as it is the second leading cause of death among the AI/AN population. CRC is the second leading cause of cancer death for AI/AN men and third leading cause of cancer death for AI/AN women.[10] There are a number of potential primary prevention activities that can be implemented to prevent colorectal cancer. Epidemiologic studies show dietary factors (fat

and fiber) may influence the onset of CRC.[11,12] Decreasing caloric intake to reduce body weight may also decrease CRC risk. Intake of calcium, vitamins A, C, D, E, and selenium has been hypothesized to reduce cancer risk.[13] Nonsteroidal anti-inflammatory drugs, particularly aspirin, are being investigated as a preventive measure to reduce the onset of CRC.[14]

Rural and Urban Classifications and Survivorship

Rural-urban classifications are often used as a proxy to measure various constructs in colorectal cancer studies. Rural-Urban classifications have been used to measure the following: access to providers, access to health care, access to screening, and risk for CRC.[15-22] However, there is lack in the consistency in how 'urban' and 'rural' are defined and a lack of clarity in describing why the chosen measure of urban/rural is a good proxy for various constructs. The classification of rural and urban can be a fluid concept and is highly dependent on the constraints one applies. Thus, using rural-urban as a proxy may result in measuring a number of factors rather than one sole factor.

When access to care is discussed, it is often referred to as an intangible concept; however, quantitative analysis necessitates a concrete measurement. For instance, rural-urban definitions are often used in models to measure access to care. Examining the issue on a theoretical level, it would seem more logical to measure distance to treatment and screening to determine access rather than categorizing individuals into rural and urban categories as a proxy for access. However, it is unclear whether a rural-urban variable versus a distance variable is a more valid measure for access to CRC related care. Therefore, it is necessary to compare the access to care constructs.

Purpose of This Study

The overall goal of this project is to determine factors that affect colon cancer survival among American Indians/Alaska Natives (AI/AN) compared to Non-Hispanic Whites (NHW). There are three specific aims to carry out the overall goal.

Specific Aim 1

Determine the research needs by reviewing the literature and identifying research gaps with respect to colorectal cancer survival among AI/AN. There have been few studies of colon cancer survival among AI/AN, so both colon and rectal cancer literature will be included. The majority of colorectal cancer studies report on epidemiologic measures, such as incidence and mortality, and have not investigated potential factors associated with colorectal cancer survival. The overall goal is to assess gaps in regards to colorectal cancer survival and offer recommendations for future research.

Specific Aim 2

Determine whether comorbidities[1] as defined by the Charlson Comorbidity Index and race are associated with poor colon cancer survival. Individuals with comorbid conditions may not be eligible for aggressive treatment schedules because having a co-morbid condition affects treatment decisions and can affect recovery. The hypothesis is that those with one or more comorbid conditions will have worse survival outcomes than those with no comorbid conditions, after controlling for confounders and adjusting for covariates. A second research hypothesis is that survival disparities among AI/AN compared to NHW will persist even when controlling for comorbidities.

[1] The Charlson Index includes the following comorbidities: prior myocardial infarct, presence of congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor, leukemia, lymphoma, moderate or severe liver disease, mestatic solid tumor, and AIDS.

Specific Aim 3

Determine if geographic access and race are associated with poor colon cancer survival. Geographic access will be defined as travel times to treatment (chemotherapy, radiation, and surgery) and travel times to screening (colonoscopy and sigmoidoscopy). The research hypothesis of this aim is that those living 60 miles or more from a treatment or screening facility will have worse colon cancer survival outcomes than those having to travel less. A secondary research hypothesis is that AI/AN will have worse outcomes than NHW after adjusting for various controls.

Methods

The first aim uses systematic review methods to determine risk factors for colorectal cancer mortality and all-cause mortality among colorectal cancer patients. The second and third aims are both retrospective cohort studies. Cox Proportional Hazards modeling was used to determine the effect that comorbidities, geographic accessibility and race has on colon cancer survival.

Summary

A more in-depth discussion about the methods used for each specific aim, results and conclusions can be found in Chapters 2, 3, and 4. Chapter 5 includes the overall conclusions for each chapter.

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CHAPTER 2

COLORECTAL CANCER MORTALITY RISK FACTORS FOR AMERICAN INDIAN/ALASKA NATIVES: A SYSTEMATIC REVIEW

Abstract

There have been few published studies about colorectal cancer (CRC) among the American Indian/Alaska Native (AI/AN) population. The studies that report on epidemiologic measures, such as incidence, mortality, and survival, among AI/AN have not fully investigated potential risk factors for mortality among those diagnosed with colorectal cancer. The overall goal is to assess knowledge gaps in CRC mortality risk factors among AI/AN by conducting a systematic review of the literature, comparing the AI/AN literature to what is known for Whites, and to offer recommendations for future research.

A systematic review was conducted in two phases. First, a search was conducted to find published systematic reviews in the area of risk factors for CRC mortality among adult AI/AN and White populations. A second search was conducted for primary literature on the same topic.

The results indicate that race was the only risk factor explored for AI/AN, whereas the literature for Whites and Non-Hispanic Whites explores a number of risk factors, which can be categorized into 6 groups: Demographic/Clinical, Lifestyle, Health

System, Treatment, Tumor Biology, and Genetic Factors. The gap in knowledge of known or suspected risk factors that contribute to risk between AI/AN and Whites/NHW demonstrate the need for more research.

Introduction

Cancer is a public health concern for the American Indian/Alaska Native (AI/AN) population because it is the second leading cause of morbidity and mortality for AI/AN men and women.[1-3] Cancer mortality in general has been examined in various regions of the United States among AI/AN but on a limited basis; and even fewer studies that examine risk for colorectal cancer (CRC) mortality among AI/AN. Previous studies suggest risk for CRC mortality among AI/AN to be greater than Whites or Non-Hispanic Whites (NHW).[4-8] A temporal analysis also demonstrated greater risk for CRC mortality for AI/AN than NHW and worse outcomes for AI/AN women and men in comparison to their NHW counterparts.[4] After controlling for stage and age at diagnosis, risk for CRC mortality is still greater for AI/AN than Whites.[4-6,8]

There is a scarcity of AI/AN research that examines CRC survivorship and thus, there is a little information on risk factors that affect CRC mortality among AI/AN. The aims of this study are to: (1) conduct a systematic review of the available literature that identifies risk factors for mortality among AI/AN and Whites and (2) conduct a comparison between the AI/AN and Whites to identify potential risk factors for further exploration, which will increase our understanding the burden of CRC among AI/AN. Cataloging the risk factors associated with mortality among AI/AN and NHW will guide the direction of future research to explain mortality patterns among AI/AN.

Methods

A systematic review of the literature was conducted in two phases. The first phase searched for published systematic reviews in the area of risk factors for CRC mortality among adult AI/AN and White populations. The second phase involved a search for primary literature on the same topic.

Systematic Review Search

The search for reviews and meta-analyses were conducted in Medline and CINAHL for the White and AI/AN populations, and additionally, in the Native Research Database for the AI/AN population. If reviews were found, they were examined for topic and content and determined if the review needed to be updated or modified.[9]

PubMed was the interface used to access Medline. Medical Subject Headings (MeSH) and synonyms were used to find studies related to the topic. PubMed uses MeSH terms to index articles and MeSH terms provide a consistent way to retrieve information. MeSH terms for this study were developed using the National Library of Medicine's MeSH database found in the PubMed Advance Search. Synonyms were developed by the author and also McKibbon.[10] See Table 2.1 for MeSH terms and synonyms.

In conjunction with the MeSH terms and synonyms, the following algorithm was entered into the PubMed search window to find systematic reviews and meta-analysis articles: Meta-analysis[pt] OR Meta-anal*[tw] OR Metaanal*[tw] OR quantitativ* review* OR quantitative* overview*[tw] OR systematic* review* OR systematic* overview*[tw] OR methodologic* review* OR methodologic* overview*[tw] OR review[pt] AND medline[tw]. Two searches were conducted to find systematic review

Table 2.1: MeSH Terms and Synonyms for Medline and CINAHL

Question Part	Question Term	Medline (MeSH Terms)	Medline (Synonyms)	CINAHL (Headings)	CINAHL (Synonyms)
Population	AI/AN	Indians, North American	"American Indian" "Native American"	“Native Americans”	"American Indian" "Native American"
	White	European Continental Ancestry Group	White	Whites	“Caucasian” “Non-Hispanic White”
Study Factor	Colorectal Cancer	Colorectal Neoplasms	"Colorectal Cancer" "Bowel cancer"	“Colorectal Neoplasms”	"Colorectal cancer" "Bowel cancer"
	Risk Factors	Risk Factors	Risk Factors	Risk Factors	Risk Factors
Outcome	Mortality	Mortality	“Cause of Death”[10] “Survival Rate”[10]	Mortality	“Cause of Death” “Survival Rate”
Ideal Design	Survival Analysis	“Survival Analysis” “Survival” “Survival Rate”	"Survival Analysis”[10]	“Survival Analysis”	“Cox Proportional Hazards Model” [10]“Kaplan-Meier Estimator”[10] “Log-rank Test”[10]

articles. An initial search used synonyms in conjunction with the algorithm and a second search used MeSH terms with the algorithm.

The interface, EBSCO, was used to conduct searches in the CINAHL database, limiting searches specifically for "systematic reviews" and CINAHL Subject Headings. Synonyms were developed by the author and also by McKibbon.[10] Table 2.1 provides CINAHL headings and synonyms used to find articles that reflect the topic. Two searches were conducted to find systematic review articles in the CINAHL database. One search used synonyms and the other used subject headings; both methods were contained with the algorithm in conjunction with the two searches.

The Native Research Database was utilized to search for systematic reviews for AI/AN. The MeSH term search only used the colorectal cancer study factor term, "colorectal neoplasm." There were very few AI/AN colorectal cancer articles and a more stringent search using all MeSH terms related to the topic areas would immediately eliminate all literature. The same was true for synonyms. Synonyms that were used for the colorectal cancer study factor were "colorectal cancer" and "bowel cancer." Table 2.2 lists the MeSH terms and synonyms for the search in the Native Research Database.

Published Primary Literature Search

The following databases were used to search for primary studies: Medline, CINAHL and the Native Research Database (AI/AN only). Search methodology mirrored the systematic search, except the algorithm and other methods used to find reviews were omitted.

Table 2.2: MeSH Terms and Synonyms for the Native Health Database

Question Part	Question Term	Native Health Database (MeSH Terms)	Native Health Database (Synonyms)
Population	AI/AN	Nonapplicable	Nonapplicable
Study Factor	Colorectal Cancer	Colorectal Neoplasm	"Colorectal Cancer" "Bowel cancer"
	Risk Factors	Risk Factors	Risk Factors
Outcome	Mortality	Mortality	"Cause of Death"[10] "Survival Rate"[10]
Ideal Design	Survival Analysis	"Survival Analysis" "Survival" "Survival Rate"	"Survival Analysis"[10]

Inclusion Criteria

Inclusion criteria were as follows: studies that included a White population, AI population, AI/AN population, United States population, and published in English. All publication years were included in the search. A population that was 18 years of age and over was also included in the selection of articles. Outcome for the studies were all-cause mortality, colon cancer mortality, and colorectal cancer mortality.

Three of the studies included in this review used all-cause mortality as the outcome measure and they used various non-SEER data.[11-13] Although there was no clear rationale behind choosing all-cause mortality instead of cancer-specific mortality, these studies were included in the review because their focus was CRC mortality. The results will have to be viewed as an approximation for colon and/or rectal cancer mortality.

Exclusion Criteria

Exclusion criteria include studies with a solely Alaska Native focus and studies that focus on HNPCC, FAP, Peutz-Jeghers syndrome, Cowden's syndrome, and hereditary mixed polyposis.

Quality Appraisal

The author was the sole reviewer of the literature and was responsible for selecting and omitting studies. Dissertation committee members also gave input into whether particular articles should be included or not. Endnote X4 (Thomson Reuters, Philadelphia, PA) was used to de-duplicate articles.

Literature Selection Results

The systematic review search for the White population retrieved one article by Berry, *et al*.[14] The article by Berry, *et al.* reported on survival and colorectal screening proportions and also gave a descriptive report on cancer stage, colorectal cancer screening, and colorectal cancer treatment. Since the article did not report on risk factors for CRC, it was excluded.

The search for primary articles in Medline and CINAHL retrieved 221 articles, of which 16 articles were included in the final review. No articles were reviewed in the search for AI/AN systematic reviews. The search for primary articles resulted in 4 articles for the final review (Table 2.3).

Table 2.3: Results of Systematic Review and Primary Literature Search

	Whites: Systematic Reviews	Whites: Primary Literature	AI/AN: Systematic Reviews	AI/AN: Primary Literature
PubMed: Synonyms	0	46	0	6
PubMed: MeSH	1	243	0	14
CINAHL: Synonyms	0	0	0	1
CINAHL: MeSH	0	84	0	2
Native Health Database: Synonyms	N/A	N/A	0	18
Native Health Database: MeSH	N/A	N/A	0	14
Total after de-duplication	1	221	0	32
Total Reviewed	0	16	0	4

Results

AI/AN Risk Factors

The search for AI/AN primary articles resulted in four articles[4,5,15,16] which had very limited information in regards to risk factors for CRC survival. Interestingly, the relevant literature revealed that race defined as AI/AN was the only risk factor explored (Table 2.4). Studies suggest that the risk for all-cause and CRC mortality is higher among the AI/AN than the NHW population. Results also demonstrated that AI/AN are at higher risk for CRC mortality than NHW when diagnosed at later stages[15]. There appears to be no difference in CRC mortality risk between AI/AN in the early stage group (HR=1.20, CI=0.90-1.80) than the later stage group (HR=1.20, CI=1.00-1.40)[15]. Studies also suggest that AI/AN men and women have a higher risk for CRC mortality than their NHW counterparts,[4,5] with CRC mortality risks among AI/AN men and women ranging from 10% -14% and 38% - 50% higher than for NHW men and women, respectively[4,5]. These

Table 2.4: Race as a Risk Factor for Colorectal Cancer and All-Cause Mortality among American Indians/Alaska Natives

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[a]Sugarman, et al. [1994][16]			Race	NHW	1.00	110,899	Age, stage, and sex.
				AI SEER Coded	1.30 (1.00, 1.60)	451	
				AI SEER or IHS Code	1.20 (1.00, 1.60)	551	
[b]Chien, et al. [2005][15]	1		Race	NHW	1.00	120,491	Age at diagnosis, year of diagnosis, SEER registry, surgical treatment (Y/N), radiation treatment, stage at diagnosis, and Tumor Stage.
				AI	1.20 (1.00, 1.40)	437	
	2	Tumor Stage I & II	Race	NHW	1.00	68,641	Age at diagnosis, year of diagnosis, SEER registry, surgical treatment (Y/N), radiation treatment, and stage at diagnosis.
				AI	1.20 (0.90, 1.80)	220	
	3	Tumor Stage III & IV	Race	NHW	1.00	51,850	Age at diagnosis, year of diagnosis, SEER registry, surgical treatment (Y/N), radiation treatment, and stage at diagnosis.
				AI	1.20 (1.00, 1.40)	217	
[b]Clegg, et al. [2002][4]	1	Sex: Males	Race	NHW	1.00	95,455	Age and tumor stage
				AI/AN	1.10 (0.86, 1.50)	259	
	2	Sex: Females	Race	NHW	1.00	95,313	Age and tumor stage.
				AI/AN	1.50 (1.10, 1.90)	222	

Table 2.4: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[b]Jemal, et al. [2004][5]	1	Sex: Males	Race	NHW	1.00	No.[c]	Age and tumor stage.
				AI/AN	1.14 (0.95, 1.35)		
	2	Sex: Females	Race	NHW	1.00	No.[c]	Age and tumor stage.
				AI/AN	1.38 (1.16, 1.64)		

[a]Results are for all-cause mortality
[b]Results are for colorectal cancer mortality
[c]No sample size given.

findings suggest that like NHWs, race, sex, and stage are potential risk factors for all-cause/CRC mortality among the AI/AN population.

White/NHW Risk Factors

Risk factors for mortality among the White population have been explored more extensively than the AI/AN population. Risk factors, based on the literature, for mortality among the White population can be grouped into 6 general categories: demographic/clinical factors, lifestyle factors, health system factors, treatment factors, tumor biology factors, and genetic factors (Table 2.5).

Demographics and Clinical Factors

The majority of the studies, which examined racial disparities, concluded that the White population is at lower risk for CRC, colon, and all-cause mortality than African Americans (Table 2.6).[11,13,17-21] Risk for CRC, colon, or all-cause mortality for the White population ranged from 40% to 88% less than African Americans. Results are mixed for Hispanic groups as the literature shows both an increased and decreased risk for CRC and all-cause mortality for Hispanics when compared to Whites.[13,22,23] The data suggest that Pacific Islander men and women have lower risk for CRC mortality than the White population.[22] However, the results were not statistically significant. One study compared survival outcomes between Filipino-Americans, Philippine population, and Whites.[24] The results found that Non-Hispanic Whites (HR=1.12, CI=1.04-1.20) and the Philippine population (HR=2.30, CI=1.83-2.25) had higher risk for CRC mortality than Filipino-Americans.[24]

When examining if there are differences by race, stage, and tumor grade, the

Table 2.5: Categorization of Colorectal Cancer Mortality Risk Factors for the White/NHW Population

Category	Risk Factors
Demographic/Clinical Factors	Race, Age, Sex, Year of Diagnosis, SEER Region, Education Level, Poverty Index/Status, Median Income, SES (Income & Education), Marital Status, Urban/Rural Residence, Bowel Obstruction, and Comorbidities
Lifestyle Factors	Smoking Status
Health System Factors	Insurance Type, Facility Type
Treatment Factors	First Course Therapy, Surgery, Standard Therapy Received, Radiotherapy, Treatment Modality (Surgery, Radiation, Chemotherapy)
Tumor Biology Factors	SEER[1] Summary Stage, TNM Stage, TNM Staging Components, Cancer Site, Cancer Size, Histology or Morphology, Tumor Differentiation, Histological Grade
Genetic Factors	GSTM1 Gene, GSTT1 Gene, GSTP1 Gene, Codon 72 Polymorphisms, Bcl-2 Expression, P53 Status, Nuclear Accumulation of p53

[1] Surveillance Epidemiology and End Results Program

Table 2.6: Race as a Predictor for Colorectal and Colon Cancer and All-Cause Mortality among White/NHW and Other Populations

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[a]Alexander, et al. [2004][17]	1	All Stages	Race	White	1.00	292	Age, gender, hospital, tumor stage, degree of tumor differentiation, tumor anatomic subsite, and anatomic tumor site.
				AA	1.58 (1.14-2.18)	199	
	2	Stage II	Race	White	1.00	106	Age, gender, hospital, tumor grade, anatomic subsite in the colon.
				AA	2.53 (1.31-4.86)	72	
	3	Stage III	Race	White	1.00	88	Age, gender, hospital, tumor grade, anatomic subsite in the colon.
				AA	1.21 (0.70-2.12)	54	
	4	Stage IV	Race	White	1.00	38	Age, gender, hospital, tumor grade, anatomic subsite in the colon.
				AA	1.44 (0.78-2.64)	32	
[a]Alexander, et al. [2005][18]	1	Low Grade Tumor	Race	White	1.00	190	Race, age, gender, treatment hospital, tumor anatomic subsite, pathologic tumor stage, tumor grade, and race X tumor grade interaction.
				AA	1.27 (0.87-1.83)	143	
	2	High Grade Tumor	Race	White	1.00	39	Race, age, gender, treatment hospital, tumor anatomic subsite, pathologic tumor stage, tumor grade, and race X tumor grade interaction.
				AA	3.05 (1.32-7.05)	26	
[b]Govindarajan, et al. [2003][11]			Race	White	1.00	427	Unknown
				AA	1.50 (1.20, 1.90)	190	

Table 2.6: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Jones, et al. [2009][25]	1		Race	White AA	1.00 1.85 (1.18, 2.91)	184 131	Age, gender, TNM stage at diagnosis, self-rated health, smoking status, and receipt of chemotherapy.
	2		Race	White AA	1.00 1.82 (1.15, 2.89)	117 74	Age, gender, TNM stage at diagnosis, self-rated health, smoking status, receipt of chemotherapy, and GSTM1 genotype.
	3		Race	White AA	1.00 1.79 (1.13, 2.84)	120 76	Age, gender, TNM stage at diagnosis, self-rated health, smoking status, receipt of chemotherapy, and GSTT1 genotype.
	4		Race	White AA	1.00 1.89 (1.21, 2.98)	116 77	Age, gender, TNM stage at diagnosis, self-rated health, smoking status, receipt of chemotherapy, and GSTP1 genotype.
Marcella, et al. [2001][19]			Race	White AA	1.00 1.19 (1.09, 1.30)	58,020 2,784	Age, gender, sex, race X sex interaction term, stage, anatomic site, grade, education.

Table 2.6: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[a]Mayberry, et al. [1995][20]			Race	White	1.00	521	Education, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, distant metastasis, and surgery.
				AA	1.50 (1.20-1.90)	454	
Niu, et al. [2010][22]	1	Male	Race	White	1.00	27,005	Poverty status.
				Black	1.13 (1.02, 1.25)	2,561	
				API	0.99 (0.78, 1.26)	381	
				Hispanic	0.91 (0.79, 1.05)	1299	
	2	Female	Race	White	1.00	26,291	Poverty status.
				Black	1.15 (1.04, 1.26)	2,924	
				API	0.84 (0.64, 1.10)	289	
				Hispanic	0.95 (0.84, 1.08)	1,357	
Potosky, et al. [2002][23]			Race	AA	1.00	16	Standard therapy received, year of diagnosis, age at diagnosis, sex, SEER region, marital status, median income, cancer site, tumor extent, nodal status, histologic grade, and comorbidities.
				White	0.94 (0.55, 1.04)	171	
				Hispanic	0.84 (0.37, 1.11)	9	

Table 2.6: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Redaniel, et al. [2010][24]	2		Race	Filipino-Americans	1.00	2,671	Age, sex, stage, morphology, surgery, and radiotherapy.
				NHW	1.12 (1.04, 1.20)	133,551	
				Philippine	2.03 (1.83, 2.25)	1,635	
[b]Roetzheim, et al. [2000][13]			Race	NHW	1.00	8,138	Age, sex, marital status, insurance payer medicare, insurance payer non-medicare, education level, median income level, place of residence, anatomic site, comorbidity index, smoking status, stage at diagnosis, and treatment modality.
				NHAA	1.18 (1.01, 1.37)	575	
				Hispanic	1.11 (0.97, 1.27)	754	
				Other	0.58 (0.37, 0.92)	84	
Yan, et al. [2009][21]			Race	White	1.00	7,215	Age, sex, marital status, socioeconomic status, tumor grade, TNM stage, and surgical treatment.
				AA	1.06 (0.94, 1.19)	1,863	

[a]Results are for colon cancer mortality
[b]Results are for all-cause mortality
[c]Model 1: covariates include age, gender, TNM stage at diagnosis, self-rated health
[d]Model 1 + GSTM1 genotype
[e]Model 1 + GSTT1 genotype
[f]Model 1 + GSTP1 genotype

White population had lower risk for colon cancer mortality than African Americans.[17,18] At Stage II, III, or IV, the White population's risk for colon mortality was 40% to 83% lower than African Americans.[17] The White population (HR=1.00) also had lower risk by high tumor grade for colon cancer mortality than African Americans (3.05, CI=1.32-7.05).[18] White males and females have lower risks for CRC mortality than their African Americans counterparts (Males: HR=1.13, CI=1.02-1.25; Females: HR=1.15, CI=1.04-1.26).[22]

The studies that included sex as a predictor found males to be at higher risk for all-cause and CRC mortality than women (Table 2.7). Three of the six studies examining sex had results that were statistically significant,[13,19,22] ranging from HR=0.84 (CI=0.78-0.92) to HR=0.92 (CI=0.86-0.99) for all-cause and CRC mortality.

Studies that examined marital status found that those who are married were at 10% to 21% less risk for mortality than those who are not married (Table 2.8).[13,21] Age as expected, a predictor for mortality with older patients, having higher risk for CRC, colon, and all-cause mortality (Table 2.9).

A number of studies included at least one measure of socio-economic status (SES) as a predictor for mortality. Reporting risks for mortality using measures of education, income, and employment status (Table 2.10). The majority of the results for income as a risk for all-cause, CRC, or colon mortality were not statistically significant.[12,13,20,22,23] However, the results suggest that the poorer one is, the greater risk for CRC, colon, and all-cause mortality.[12,13,20,22,23] The data also suggest that men and women who fall at or more than 20% poverty level, have a 37% and 20% increase in risk for CRC, respectively.[22]

Table 2.7: Sex as a Predictor for Colorectal Cancer and All-Cause Mortality among the White/NHW Population

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Marcella, et al. [2001][19]			Sex	Male	1.00	31,012	Age, race, gender, race X sex interaction term, stage, anatomic site, grade, education.
				Female	0.91 (0.88, 0.94)	30,792	
Pagano, et al. [2003][26]	1	1960-1974	Sex	Male	1.00	1,668	Stage at diagnosis, age, and year of diagnosis.
				Female	0.92[b]	1,211	
	2	1975-1987	Sex	Male	1.00	3,336	Stage at diagnosis, age, and year of diagnosis.
				Female	0.88[b]	2,209	
	3	1988-2000	Sex	Male	1.00	4,647	Stage at diagnosis, age, and year of diagnosis.
				Female	0.90[b]	3,353	
Potosky, et al. [2002][23]			Sex	Male	1.00	106	Standard therapy received, year of diagnosis, age at diagnosis, race, SEER region, marital status, median income, cancer site, tumor extent, nodal status, histologic grade, and comorbidities.
				Female	0.86 (0.70, 1.06)	94	
Redaniel, et al. [2010][24]			Sex	Male	1.00	69,273	Age, race, stage, morphology, surgery, and radiotherapy.
				Female	1.00 (0.98, 1.01)	68,584	
[a]Roetzheim, et al. [2000][13]			Sex	Male	1.00	4,875	Age, race, marital status, insurance payer medicare, insurance payer nonmedicare, education level, median income level, place of residence, anatomic site, comorbidity index, smoking status, stage at diagnosis, and treatment modality.
				Female	0.92 (0.86, 0.99)	4,673	

Table 2.7: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Yan, et al. [2009][21]			Sex	Male	1.00	4,666	Age, race, marital status, socioeconomic status, tumor grade, TNM stage, and surgical treatment.
				Female	0.84 (0.78, 0.92)	4,412	

[a]Results are for all-cause mortality
[b]Not significant at the p<0.005

Table 2.8: Marital Status as a Predictor for Colorectal Cancer Mortality among the White/NHW Population

Study	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Potosky, et al. [2002][23]	Marital Status	Married Other	1.00 1.24 (1.00, 1.54)	121 79	Standard therapy received, year of diagnosis, age at diagnosis, race, sex, SEER region, median income, cancer site, tumor extent, nodal status, histologic grade, and comorbidities.
Roetzheim, et al. [2000][13]	Marital Status	Married Not Married	0.90 (0.83, 0.97) 1.00	5,719 3,620	Age, sex, race, insurance payer medicare, insurance payer nonmedicare, education level, median income level, place of residence, anatomic site, comorbidity index, smoking status, stage at diagnosis, and treatment modality.
Yan, et al. [2009][21]	Marital Status	Married Other	1.00 1.26 (1.15, 1.37)	4,963 3,810	Age, sex, race, socioeconomic status, tumor grade, TNM stage, and surgical treatment.

Table 2.9: Age as a Predictor for Colorectal and Colon Cancer and All-Cause Mortality among the White/NHW Population

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Chatla, et al. [2005][27]	1	Stage II	Age	<65	1.00	43	Gender, Bcl-2 expression, pT component of stage, tumor location, tumor differentiation, and tumor size.
				>=65	1.08 (0.36, 3.22)	49	
	2	Stage III	Age	<65	1.00	30	Gender, Bcl-2 expression, pN component of stage, pT component of stage, tumor location, tumor differentiation, and tumor size.
				>=65	1.74 (0.70, 4.34)	36	
[b]Govindarajan, et al. [2003][11]			Age	<60	1.00	No.[d]	Race and stage.
				>=60	1.40 (1.10, 1.70)		
[a]Jessup, et. al. [2005][28]			Age	<60	1.00	6,220	Race, sex, histological grade, anatomic subsite, AJCC substage, surgery, and adjuvant chemotherapy.
				60-69	1.19 (1.14, 1.25)	6,293	
				70-79	1.56 (1.49, 1.62)	8,189	
				>=80	2.24 (2.14, 2.35)	5,898	
Manne, et al. [1998][29]			Age	<65	1.00	230	Gender, tumor location, tumor size, differentiation, pT component of stage, pN component of stage, pM component of TNM stage, and nuclear accumulation of p53.
				>=65	2.86 (1.47, 5.60)	274	
Marcella, et al. [2001][19]			Age	20-29	0.67 (0.58, 0.77)	No.[d]	Race, gender, sex, race X sex interaction term, stage, anatomic site, grade, education.
				40-59	0.86 (0.82, 0.90)		
				60-79	1.00		
				80+	1.42 (1.37, 1.47)		

Table 2.9: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Pagano, et al. [2003][26]	1	1960-1974	Age	10 yr. increments	1.20[c]	2879	Stage, sex, and year of diagnosis.
	2	1975-1987		10 yr. increments	1.17[c]	5545	Stage, sex, and year of diagnosis.
	3	1988-2000		10 yr. increments	1.17[c]	8000	Stage, sex, and year of diagnosis.
Potosky, et al. [2002][23]			Age	80+	1.00	37	Standard therapy received, year of diagnosis, race, age at diagnosis, sex, SEER region, marital status, median income, cancer site, tumor extent, nodal status, histologic grade, and comorbidities.
				75-79	0.59 (0.41, 0.83)	29	
				65-74	0.58 (0.43, 0.79)	66	
				55-64	0.54 (0.39, 0.74)	40	
				<=55	0.55 (0.38, 0.80)	28	
Redaniel, et al. [2010][24]			Age	<50	1.00	9,429	Sex, stage, morphology, surgery, and radiotherapy.
				50-59	1.04 (0.99, 1.09)	16,545	
				60-69	1.28 (1.23, 1.34)	29,526	
				70-79	1.75 (1.68, 1.83)	44,727	
				80+	3.08 (2.96, 3.21)	37,680	
[b]Robbins, et al. [2009][12]			Age	18-49	1.00	16,643	Insurance status, stage, facility type, neighborhood education level and neighborhood income level and number of comorbidities.
				50-55	1.11 (1.03, 1.19)	16.332	
				56-60	1.23 (1.15, 1.32)	16.726	
				61-64	1.37 (1.28, 1.47)	14.650	

Table 2.9: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[b]Roetzheim, et al [2000][13]			Age		1.03 (1.025, 1.035)	No.[d]	Race, sex, marital status, insurance payer medicare, insurance payer non-medicare, education level, median income level, place of residence, anatomic site, comorbidity index, smoking status, stage at diagnosis, and treatment modality.
Yan, et al [2009][21]			Age	<49	1.00	566	Race, sex, marital status, socioeconomic status, tumor grade, TNM stage and surgical treatment.
				49-64	1.17 (0.99, 1.39)	2,321	
				>64	1.37 (1.17, 1.62)	6,191	

[a]Results are for colon cancer mortality
[b]Results are for all-cause mortality
[c]Significant at the $p<0.0001$
[d]Sample sizes are not reported for this variable(s).

Table 2.10: SES Measures as Predictors for Colorectal and Colon Cancer and All-Cause Mortality among the White/NHW Population

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Potosky, et al. [2002][23]			Median Income	Lowest	1.00	43	Standard therapy received, year of diagnosis, race, age at diagnosis, sex, SEER region, marital status, cancer site, tumor extent, nodal status, histologic grade, and comorbidity.
				Low Middle	1.14 (0.80, 1.49)	47	
				High Middle	0.92 (0.70, 1.21)	51	
				Highest	0.91 (0.69, 1.21)	53	
Robbins, et al. [2009][12]			Median Household Income	<$30,000	1.00	9,349	Insurance status, age, stage, facility type, neighborhood education level, and neighborhood income level and number of comorbidity.
				$30,000-$34,999	1.14 (0.80, 1.49)	11,572	
				$35,000-$45,999	0.92 (0.70, 1.21)	17,789	
				>= $46,000	0.91 (0.69, 1.21)	24,648	
Roetzheim, et al. [2000][13]				Median Income Level	0.99 (0.94, 1.03)	No.[c]	Age, race, sex, marital status, insurance payer medicare, insurance payer nonmedicare, education level, place of residence, anatomic site, comorbidity index, smoking status, stage at diagnosis, and treatment modality.

Table 2.10: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Mayberry, et al. [1995][20]			Poverty Index, %	<=125	1.0	165	Education, race, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, distant metastasis, and surgery.
				126-400	0.6 (0.4, 0.9)	230	
				>400	0.4 (0.3, 0.7)	193	
				Unknown	1.3 (1.0, 1.8)	387	
Niu, et al. [2010][22]	1	Sex: Male	Poverty Status	<5%	1.0	15,604	Race, age, and stage.
				5%-<10%	1.04 (0.97, 1.11)	8,123	
				10%-<20%	1.12 (1.03, 1.21)	5,015	
				>=20%	1.37 (1.23, 1.53)	2,504	
	2	Sex: Female	Poverty Status	<5%	1.0	14,587	Race, age, and stage.
				5%-<10%	1.05 (0.99, 1.13)	8,162	
				10%-<20%	1.07 (0.99, 1.16)	5,252	
				>=20%	1.20 (1.08, 1.34)	2,791	
Mayberry, et al. [1995][20]			Education (years)	<=8	1.0	174	Education, race, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, distant metastasis, and surgery.
				9-11	1.0 (0.7, 1.6)	100	
				12	0.8 (0.6, 1.3)	183	
				>12	0.6 (0.4, 0.9)	232	
				Unknown	2.2 (1.6-3.1)	286	

Table 2.10: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Robbins, et al. [2009][12]			w/o H.S. Degree	<=14.0%	1.00	22,558	Insurance status, age, stage, facility type, neighborhood education level and neighborhood income level, and number of comorbidities.
				14.0%-19.9%	1.14 (1.07, 1.22)	15,108	
				20%-28.9%	1.14 (1.07, 1.22)	15,680	
				>=29.0%	1.17 (1.06, 1.29)	11,015	
Roetzheim, et al. [2000][13]			Education Level	<H.S.	1.20 (1.00, 1.45)	363	Age, race, sex, marital status, insurance payer medicare, insurance payer nonmedicare, education level, median income level, place of residence, anatomic site, comorbidity index, smoking status, stage at diagnosis, and treatment modality.
				>=HS Graduate	1.00	9,130	
Marcella, et al. [2001][19]			SES	Bottom Quartile of H.S. Grads	1.09 (1.04, 1.15)	No.[c]	Age, race, gender, sex, race X sex interaction term, stage, anatomic site, grade, education.
				Middle 2 Quartiles of H.S Grads	1.05 (1.01, 1.09)		
				Upper Quartile of H.S Grads	1.00		
				Unemployment >10%	1.05 (1.00, 1.11)		

Table 2.10: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Yan, et al. [2009][21]			SES	Poor	1.00	No.[c]	Age, race, sex, marital status, tumor grade, TNM stage, and surgical treatment.
				Working Poor	1.19 (1.05, 1.35)	2034	
				Working, Non-Poor, under-educated	1.12 (1.01, 1.25)	1947	
				Working, Non-Poor, Educated	0.99 (0.88, 1.11)	1706	

[a]Results are for colon cancer mortality
[b]Results are for all-cause mortality
[c]Sample sizes are not reported for this variable(s).

Less education was also found to be a significant predictor for increased all-cause mortality (Table 2.10), with risks being the largest in the neighborhood group that had the highest percentage of individuals without a high school degree.[12] A combination of being employed, nonpoor and under-educated also a increases one's risk for CRC mortality by 12%.[21] Yan, *et al.* found that the working poor who were under-educated had the highest risk for CRC mortality (H.R.=1.19, CI=1.05-1.35).[21]

Residence and year of diagnosis as predictors for mortality among non-AI/AN were also not statistically significant (Table 2.11). However, the results suggest that risk for CRC mortality is higher in the regions of Connecticut (HR=1.04, CI=072-1.49), New Mexico (HR=1.15, CI=0.65-2.04), and Seattle (HR=1.23, CI=0.86-1.74) than in the other SEER regions.[23] The Los Angeles SEER region (HR=0.80, CI=0.47-1.34) potentially has the least risk for mortality, followed by Iowa, Atlanta, and Utah. The lack of significance may be due to low sample size for each area.

Urban and rural residency may also be an indicator for mortality. One study, not statistically significant, suggests that urban residents are at less risk (HR=0.98, CI=0.91-1.05) for all-cause mortality than nonurban residents.[13] The lack of rural-urban residence may be due to the statistical model having specific covariates that measure disparities. For instance, this model also included insurance status, income level, and education, which could be predictors for rural-urban status.

The results from year of diagnosis were not statistically significant, but they suggest increased CRC mortality as the year of diagnosis increases.[23,26] Again, low sample size may be the reason for nonsignificant results.

Clinical predictors, such as bowel obstruction and comorbidity, can be found in

Table 2.11: Other Predictors for Colorectal Cancer and All-Cause Mortality among the White/NHW Population

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Potosky, et al. [2002][23]			SEER Region	San-Francisco/ Oakland	1.00	27	Standard therapy received, year of diagnosis, race, age at diagnosis, sex, marital status, median income, cancer site, tumor extent, nodal status, histologic grade, and comorbidity.
				Los Angeles	0.80 (0.47, 1.34)	18	
				Iowa	0.84 (0.60, 1.20)	31	
				Atlanta	0.88 (0.56, 1.38)	11	
				Utah	0.95 (0.62, 1.43)	6	
				Detroit	1.00 (0.73, 1.38)	38	
				Connecticut	1.04 (0.72, 1.49)	35	
				New Mexico	1.15 (0.65, 2.04)	9	
				Seattle	1.23 (0.86, 1.74)	26	
[a]Roetzheim, et al. [2000][13]			Residence	Urban	0.98 (0.91, 1.05)	5,019	Age, race, sex, marital status, insurance payer medicare, insurance payer non-medicare, education level, median income level, anatomic site, comorbidity index, smoking status, stage at diagnosis, and treatment modality.
				Non-urban	1.00	4,532	
Pagano, et al. [2003][26]	1	1960-1974	Year of Diagnosis	10 year increments	0.65[b]	No.[d]	Age, stage, and sex.
	2	1975-1987	Year of Diagnosis	10 year increments	0.87[c]	No.[d]	Age, stage, and sex.
	3	1988-2000	Year of Diagnosis	10 year increments	0.99[c]	No.[d]	Age, stage, and sex.

Table 2.11: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Potosky, et al. [2002][23]			Year of Diagnosis	1990	1.00	68	Standard therapy received, race, age at diagnosis, sex, SEER region, marital status, median income, cancer site, tumor extent, nodal status, histologic grade, and comorbidity.
				1991	0.85 (0.68, 1.06)	69	
				1995	1.06 (0.79, 1.42)	64	

[a]Results are for all-cause mortality
[b]Significant at the $p<0.0001$
[c]Not significant at the $p<0.005$
[d]Sample sizes are not reported for this variable(s).

Table 2.12. Bowel obstruction was the only clinical characteristic that was examined as a predictor for mortality (Table 2.12). Risk for colon cancer mortality was high if one had bowel obstruction or perforation and required emergency surgery compared to those who had no bowel obstruction (HR.=2.5, CI=1.6-4.2).[20]

Various studies used different measures to examine the effect of comorbidity, including amount (number) of comorbidity and level of severity. Results indicate that having one comorbidity increases your risk for all-cause mortality by 12%, two comorbidity increases risk by 32%, three or more increases by 48%.[12] Based on the Roetzheim's study, which takes severity of diseases into account, one comorbidity increases risk for all-cause mortality by 22%, but increases to 52%.[13]

Lifestyle Factors

Lifestyle factors can also impact colon cancer, colorectal cancer, or all-cause mortality. Only one study included a lifestyle factor to examine the impact on all-cause morality. Smoking status was the only lifestyle factor that was examined. After controlling for several variables, smoking status demonstrated a negative effect on survival. Smokers are at a higher risk (HR=1.13, CI=1.03-1.24) for all-cause mortality than nonsmokers (Table 2.13).[13]

Health System Factors

In general, individuals who are uninsured or have public insurance are at higher risk for mortality than those with private insurance (Table 2.14). In comparison to having private insurance, the uninsured had the greatest risk for all-cause mortality (41%) and colon cancer mortality (76%).[12,13,20] Medicare recipients did not fair well in comparison

Table 2.12: Clinical Factors that Predict Colorectal and Colon Cancer and All-Cause Mortality among the White/NHW Population

Study	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[a]Mayberry, et al. [1995][20]	Bowel Obstruction	No	1.00	No.[c]	Education, race, poverty index, type of insurance, number of comorbid conditions, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, distant metastasis, and surgery.
		Yes/NOS	1.80 (1.30, 2.40)		
		Yes/ perforation	2.50 (1.60, 4.20)		
		Unknown	0.80 (0.40, 1.60)		
[a]Mayberry, et al. [1995][20]	No. of comorbid conditions	0	1.0	376	Education, race, poverty index, type of insurance, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, distant metastasis, and surgery.
		1	1.1 (0.8, 1.4)	310	
		>=2	1.1 (0.9, 1.2)	289	
Potosky, et al. [2002][23]	Comorbidities	>=2	1.00	8	Standard therapy received, year of diagnosis, race, age at diagnosis, sex, SEER region, marital status, median income, cancer site, tumor extent, nodal status, and histologic grade.
		1	0.91 (0.60, 1.38)	40	
		None	0.70 (0.48, 1.04)	152	
[b]Robbins, et al. [2009][12]	No. of comorbid conditions	0	1.00	36,441	Insurance status, age, stage, facility type, neighborhood education level, and neighborhood income level.
		1	1.12 (1.06, 1.19)	15,320	
		2	1.32 (1.23, 1.42)	8,324	
		>=3	1.48 (1.35, 1.61)	4,165	
[b]Roetzheim, et al. [2000][13]	Comorbidity Index	0	1.00	6,813	Age, race, sex, marital status, insurance payer medicare, insurance payer nonmedicare, education level, median income level, place of residence, anatomic site, smoking status, stage at diagnosis, and treatment modality.
		1	1.22 (1.12, 1.32)	1,998	
		>=2	1.52 (1.36, 1.70)	740	

[a]Results are for colon cancer mortality
[b]Results are for all-cause mortality
[c]Sample sizes are not reported for this variable(s).

Table 2.13: Lifestyle Factors that predict All-Cause Mortality among the White/NHW Population

Study	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Roetzheim, et al. [2000][13]	Smoking Status	Smoker Non-smoker	1.13 (1.03, 1.24) 1.00	1,405 8,146	Age, race, sex, marital status, insurance payer medicare, insurance payer nonmedicare, education level, median income level, place of residence, anatomic site, comorbidity index, stage at diagnosis, and treatment modality.

Table 2.14: Health System Factors that Predict Colorectal and Colon Cancer Mortality among the White/NHW Population

Study	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[a]Mayberry, et al. [1995][20]	Type of Insurance	Private Public None Unknown	1.0 1.5 (1.1, 2.1) 1.6 (0.9, 2.8) 3.1 (2.4, 4.0)	No.[C]	Education, race, poverty index, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, distant metastasis, and surgery.
[b]Robbins, et al. [2009][12]	Insurance Status	Private Medicare Medicaid Uninsured	1.00 1.77 (1.63, 1.93) 1.59 (1.47, 1.73) 1.76 (1.61, 1.93)	No.[C]	Age, stage, facility type, neighborhood education level and neighborhood income level and number of comorbidities.
[b]Roetzheim, et al. [2000][13]	Insurance Payer Medicare	Medicare FFS Medicare HMO	1.00 1.05 (0.91, 1.21)	5618 477	Age, race, sex, marital status, education level, median income level, place of residence, anatomic site, comorbidity index, smoking status, stage at diagnosis, and treatment modality.
[b]Roetzheim, et al. [2000][13]	Insurance Payer Non-Medicare	Private FFS Medicaid Private HMO Uninsured	1.00 1.44 (1.06, 1.97) 1.40 (1.18, 1.67) 1.41 (1.12, 1.77)	1251 126 702 250	Age, race, sex, marital status, education level, median income level, place of residence, anatomic site, comorbidity index, smoking status, stage at diagnosis, and treatment modality.

Table 2.14: continued

Study		Variable	Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[b]Robbins, et al. [2009][12]	Facility Type	Community cancer program	1.00	11,675	Insurance status, age, stage, neighborhood education level and neighborhood income level, and number of comorbidity.
		Comprehensive community cancer program	0.97 (0.91, 1.04)	29.060	
		Teaching/ Research	0.85 (0.79, 0.91)	21,233	
		Other	0.87 (0.76, 1.00)	2,395	

[a]Results are for colon cancer mortality
[b]Results are for all-cause mortality
[c]Sample sizes are not reported for this variable(s).

to those with private insurance or Medicaid. They had a higher risk (HR=1.77, CI=1.63-1.93) for all-cause mortality than those with private insurance (HR=1.00).[12] Those insured via Medicaid had risk ranging from HR=1.44 (CI=1.06-1.97) to HR=1.59 (CI=1.47-1.73) for all-cause mortality than those with private insurance.[12,13]

Facility type also appeared to impact all-cause mortality risk, with those treated at a Teaching/Research facility (HR=0.85, CI=0.79-0.91) experiencing lower risk than those treated at a Community Cancer program.

Treatment Factors

Cancer treatment has also been examined as a risk factor for mortality among non-AI/AN (Table 2.15). As expected, having surgery appears to have a large influence on decreased risk for CRC and colon cancer mortality.[20,24] One's risk for CRC and colon cancer mortality, if they do not have surgery, increases to a range of 2.5 to 5.19 times as those who have surgery.[20,24] Results from two studies show that having adjuvant chemotherapy, along with surgery, decreases risk for CRC (HR=0.64, CI=0.62-0.66) and colon cancer mortality (HR=0.53, CI=0.50-0.56) compared to those who only had surgery alone.[23,28] Not having radiotherapy also increases one's risk for CRC mortality by 15%.[24]

Tumor Biology

Cancer sites have been investigated as a predictor for mortality (Table 2.16). Although findings from pervious research are inconclusive in regard to tumor location (colon or rectum),[13,19,23] Chatla and colleagues (2005) suggests that the risk for CRC mortality among Stage II patients is lower for rectal tumors than for the colon tumors

Table 2.15: Treatment Factors that Predict Colorectal and Colon Cancer and All-Cause Mortality among the White/NHW Population

Study	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[a]Jessup, et. al. [2005][28]	First Course Therapy	Surgery Alone	1.00	17,046	Race, age, sex, histological grade, anatomic subsite, and AJCC substage, surgery.
		Surgery & Adjuvant Chemotherapy	0.64 (0.62, 0.66)	18,403	
		Surgery & Adjuvant Chemotherapy BRM	0.53 (0.50, 0.56)	5,315	
		Other pharmaceutical treatment	0.97 (0.92, 1.03)	2,344	
[a]Mayberry, et al. [1995][20]	Surgery	No	1.0	31	Education, race, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, and distant metastasis.
		Yes	0.4 (0.2, 0.7)	944	
Redaniel, et al. [2010][24]	Surgery	With Surgery	1.00	121	Age, sex, stage, morphology, and radiotherapy.
		Without Surgery	5.19 (5.09, 5.30)	262	
Potosky, et al. [2002][23]	Standard Therapy Received	No	1.00	Unknown	Year of diagnosis, race, age at diagnosis, sex, SEER region, marital status, median income, cancer site, tumor extent, nodal status, histologic grade, and comorbidities.
		Yes	0.87 (0.70, 1.09)		
Redaniel, et al. [2010][24]	Radiotherapy	Yes	1.00	14,738	Age, sex, stage, morphology, and surgery.
		No	1.15 (1.12, 1.18)	121,580	

Table 2.15: continued

Study	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[b]Roetzheim, et al. [2000][13]	Treatment Modality	No Surgery	1.00	7,665	Age, race, sex, marital status, insurance payer medicare, insurance payer non-medicare, education level, median income level, place of residence, anatomic site, comorbidity index, smoking status, and stage at diagnosis.
		Definitive Surgery	0.61 (0.55, 0.67)	1,877	
		No Radiation	1.00	2,449	
		Radiation Therapy	0.96 (0.88, 1.04)	9,554	
		No Chemotherapy	1.00	2,005	
		Chemotherapy	0.90 (0.83, 0.99)	9,542	

[a]Results are for colon cancer mortality
[b]Results are for all-cause mortality

Table 2.16: Cancer Site and Size Factors that Predict Colorectal Cancer and All-Cause Mortality among the White/NHW Population

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Chatla, et al. [2005][27]	1	Stage II	Tumor Location	Colon	1.00	70	Age, gender, Bcl-2 expression, pT component of stage, tumor differentiation, and tumor size.
				Rectum	0.47 (0.12, 1.87)	22	
	2	Stage III	Tumor Location	Colon	1.00	51	Age, gender, Bcl-2 expression, pN component of stage, pT component of stage, tumor differentiation, and tumor size.
				Rectum	1.19 (0.37, 3.89)	15	
Marcella, et al. [2001][19]			Anatomic Site	Right Colon	1.09 (1.05, 1.12)	20,820	Age, race, gender, sex, race X sex interaction term, SES, stage, anatomic site, grade, education.
				Left Colon	1.00	25,829	
				Rectal	1.23 (1.18, 1.28)	10,926	
				Not Specified	1.33 (1.26, 1.42)	3,834	
Mayberry, et al. [1995][20]			Anatomic Site	Distal	1.0	500	Education, race, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, distant metastasis, and surgery.
				Proximal	1.4 (1.1, 1.8)	287	
				Transverse	0.8 (0.6, 1.2)	183	
Potosky, et al. [2002][23]			Cancer Site	Colon	1.00	No.[b]	Standard therapy received, year of diagnosis, race, age at diagnosis, sex, SEER region, marital status, median income, tumor extent, nodal status, histologic grade, and comorbidities.
				Rectum	1.12 (0.92, 1.38)		

Table 2.16: Cancer Site and Size Factors that Predict Colorectal Cancer and All-Cause Mortality among the White/NHW Population

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[a]Roetzheim, et al. [2000][13]			Tumor Location	Colon	1.00	7992	Age, race, sex, marital status, insurance payer medicare, insurance payer nonmedicare, education level, median income level, place of residence, anatomic site, comorbidity index, smoking status, stage at diagnosis, and treatment modality.
				Rectum	0.98 (0.89, 1.09)	1559	
Chatla, et al. [2005][27]	1	Stage II	Tumor Size	<=5	1.00	47	Age, gender, Bcl-2 expression, tumor location, tumor differentiation, and pT component of stage.
				>5	0.52 (0.17, 1.60)	45	
	2	Stage III	Tumor Size	<=5	1.00	46	Age, gender, Bcl-2 expression, tumor location, tumor differentiation, and pT component of stage.
				>5	1.78 (0.68, 4.62)	20	

[a]Results are for all-cause mortality
[b]Sample sizes are not reported for this variable(s).

(HR=0.47, CI=0.12, 1.87).[27] It appears that there is 9% to 40% higher risk for CRC and colon cancer mortality if a tumor located on the right/proximal side of the colon rather than the left/distal.[19,20]

Tumor histology has also been examined to determine if histological characteristics affects risk for mortality (Table 2.17). People whose tumors are classified as high grade or poorly differentiated tumors have a higher risk for CRC and colon cancer mortality than those who have low grade or well-differentiated tumors.[19,20,23,24,27,28] Risk for CRC and colon cancer mortality ranges for those with high-grade tumors from 1.29 to 3.48, which is at a higher risk than those with low-grade tumors.[20,27,28] Poor tumor differentiation is also a risk for CRC and colon cancer mortality that ranges from 1.72 to 2.60 times higher than a tumor that is well differentiated.[19,20,23] Although results were not statistically significant, mucinous tumors may have a higher risk for colon cancer mortality than adenocarcinoma tumors (HR=1.40, CI=1.00-1.90).

SEER summary stage at diagnosis has also been examined as a risk factor for mortality (Table 2.18). The data strongly suggest an increased risk as cancer growth spreads throughout the body.[13,18,19,24,26] Compared to localized stage, the risk for all-cause, CRC, and colon mortality among distant cancers are 6.95 to 11.66 times higher.[13,18,19,24] Tumors classified as low or high grade also have the increased risk for colon cancer mortality at the various stages.[18] The examination of year of diagnosis groups and stage also found an increase in CRC mortality risk as cancer spreads.[26]

TNM staging is based on the extent of the tumor (T), the spread to lymph nodes (N), and distant metastasis (M) and together, the TNM characteristics are grouped into

Table 2.17: Histological Characteristics to Predict Colorectal and Colon Cancer Mortality among the White/NHW population

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Chatla, et al. [2005][27]	1	Stage II	Tumor Differentiation	Low Grade	1.00	82	Age, gender, Bcl-2 expression, pT component of stage, tumor location, tumor differentiation, and tumor size.
				High Grade	3.48 (0.35, 5.21)	20	
	2	Stage III	Tumor Differentiation	Low Grade	1.00	50	Age, gender, Bcl-2 expression, pT component of stage, tumor location, tumor differentiation, and tumor size.
				High Grade	1.29 (0.50, 3.33)	16	
[a]Jessup, et. al. [2005][28]			Histological Grade	Low	1.00	31,386	Race, age, sex, histological grade, anatomic subsite, AJCC substage, surgery, and adjuvant chemotherapy.
				High	1.41 (1.37, 1.45)	11,740	
[a]Mayberry, et al. [1995][20]			Nuclear atypia	Grade 1	1.00	237	Education, race, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, distant metastasis, and surgery.
				Grade 2	1.50 (1.10, 2.10)	375	
				Grade 3	3.10 (2.10, 4.70)	93	
				Unknown	1.50 (1.10, 2.20)	270	

Table 2.17: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
Marcella, et al. [2001][19]			Grade	Well Differentiated	1.00	8,587	Age, race, gender, sex, race X sex interaction term, SES, stage, anatomic site, grade, education.
				Moderately Differentiated	1.15 (1.10, 1.20)	31,285	
				Poorly Differentiated	1.72 (1.62, 1.82)	6,982	
				Anaplastic	2.15 (1.87, 2.46)	506	
				Unknown	1.36 (1.28, 1.43)	14,445	
[a]Mayberry, et al. [1995][20]			Grade	Well Differentiated	1.00	256	Education, race, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, distant metastasis, and surgery.
				Moderately Differentiated	1.80 (1.40, 2.50)	571	
				Poorly Differentiated	2.60 (1.70, 3.90)	108	
				Unknown	1.40 (0.70, 2.70)	40	
Potosky, et al. [2002][23]			Histologic Grade	Well Differentiated	1.00	18	Standard therapy received, year of diagnosis, race, age at diagnosis, sex, SEER region, marital status, median income, cancer site, tumor extent, nodal status, histologic grade, and comorbidities.
				Moderately Differentiated	1.33 (0.87, 2.02)	129	
				Poorly/ Undifferentiated	2.26 (1.44, 3.53)	42	
				Unknown	1.38 (0.79, 2.40)	*	

Table 2.17: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[a]Mayberry, et al. [1995][20]			Histology	Adenocarcinoma	1.00	723	Education, race, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, distant metastasis, and surgery.
				Adenocarcinoma arising in adenoma	0.20 (0.10, 0.40)	134	
				Mucinous	1.40 (1.00, 1.90)	118	
Redaniel, et al. [2010][30]			Morphology	Adenocarcinoma	1.00	90,073	Age, sex, stage, morphology, surgery, and radiotherapy.
				Others	0.72 (0.71, 0.74)	43,344	

Table 2.18: Summary Stage as a Risk Factor for Colorectal and Colon Cancer and All-Cause Mortality among the White/NHW Population

Study	Model	Stratification Variable		Variable	Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[a]Alexander, et al. [2005][18]	1	Tumor: Low Grade	Stage	Localized Stage	1.00	No.[e]	Race, age, gender, treatment hospital, tumor anatomic subsite, pathologic tumor stage and race X tumor grade interaction.
				Regional Stage	2.72 (1.74, 4.25)		
				Distant Stage	11.61 (7.21, 18.70)		
	2	Tumor: High Grade	Stage	Localized Stage	1.00	No.[e]	Race, age, gender, treatment hospital, tumor anatomic subsite, pathologic tumor stage and race X tumor grade interaction.
				Regional Stage	4.74 (1.74, 12.74)		
				Distant Stage	8.35 (3.21, 21.76)		
Marcella, et al. [2001][19]			Stage	In Situ	0.28 (0.24, 0.33)	4,191	Age, race, gender, sex, race X sex interaction term, SES, anatomic site, grade, education.
				Localized	1.00	21,730	
				Regional	2.63 (2.52, 2.75)	23,830	
				Distant	11.66 (11.14, 12.20)	9,272	
				Unknown	3.05 (2.83, 3.28)	2,754	
Pagano, et al. [2003][26]	1	Cohort: 1960-1974	Stage	Local	3.61[c]	949	Age, sex, and year of diagnosis.
				Regional	7.22[c]	1.108	
				Distant	10.83[c]	648	
	2	Cohort: 1975-1987	Stage	Local	5.25[c]	2,084	Age, sex, and year of diagnosis.
				Regional	10.50[d]	2,162	
				Distant	15.75[d]	1.041	
	3	Cohort: 1988-2000	Stage	Local	6.07[c]	3,700	Age, sex, and year of diagnosis.
				Regional	12.14[d]	2,726	
				Distant	18.21[d]	1,181	
Redaniel, et al. [2010][30]			Stage	Localized	1.00	54,873	Age, sex, morphology, surgery, and radiotherapy.
				Regional	1.56 (1.53, 1.59)	50,705	
				Distant	6.95 (6.78, 7.12)	24,915	

Table 2.18: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality (C.I.)	Sample Size	Variables Adjusted for in Model
[b]Roetzheim, et al. [2000][13]			Stage at Diagnosis	In situ	1.18 (0.94, 1.49)	612	Age, race, sex, marital status, insurance payer medicare, insurance payer non-medicare, education level, median income level, place of residence, anatomic site, comorbidity index, smoking status, and treatment modality.
				Local	1.00	2,858	
				Regional	1.98 (1.79, 2.19)	3,977	
				Distant	8.50 (7.62, 9.48)	1,486	
				Unstaged	2.74 (2.33, 3.22)	618	

[a]Results are for colon cancer mortality
[b]Results are for all-cause mortality
[c]Significant at the p<0.0001
[d]Not significant at the p<0.005
[e]Sample sizes are not reported for this variable(s).

stages ranging from I to IV, whereas summary staging, a staging system, groups cancer cases into five main categories: in situ, localized, regional, distant, and unknown.

TNM Stage groupings have also been used to determine risk for mortality (Table 2.19). Similar to summary stage, the studies examining TNM staging demonstrate increase in mortality risk with increasing disease severity, when risk for all-cause, CRC, and colon cancer mortality, in fact, increase dramatically with advancing stage, ranging from 1.84-3.30, 1.94-8.60, and 4.2-21.51 for Stage II, Stage III, and Stage IV, respectively.[11,12,20,31]

One study examined long-term mortality risk and found that as a person lives longer, his/her risk for mortality decreases. Risk for CRC mortality is higher at all stages for 2-years prior to diagnosis, in comparison to those who live up to 10 years after diagnosis.[21] When colon cancer mortality risk was examined by TNM substage, a person diagnosed at stage IIIC had a 2.95 times higher risk for mortality than someone diagnosed at substage IIIA.[28] The substages (A-C) gives a more precise description of how invasive the cancer is; substage IIIC is more severe than substage IIIA.

The individual TNM staging components have also been examined to determine if they contribute to mortality risk (Table 2.20). The T component describes the size and invasiveness of the primary tumor; the higher the T number, the larger the tumor and growth into nearby tissues. Being diagnosed with a primary tumor status of T4 increases one's risk for CRC and colon cancer mortality from HR=1.80 (CI=1.43-2.25) to HR=19.1 (CI=8.5-42.9).

The N component measures the extent of cancer spread to the lymph nodes; and while studies grouped the N components in a number of ways making it difficult to draw

Table 2.19: TNM Stage Groupings as a Risk Factor for Colorectal and Colon Cancer and All-Cause Mortality among the White/NHW Population

Study	Variable		Hazard Ratio for Mortality	Sample Size	Variables Adjusted for in Model
[a]Govindarajan, et al. [2003][11]	Stage	I	1.00	132	Age and Race.
		IV	4.20 (3.20, 5.20)	184	
Katkoori, et al. [2009][31]	Tumor Stage	I	1.00	50	Age, gender, tumor location, tumor size, codon 72 polymorphism, p53 mutation status.
		II	1.63 (0.74, 3.59)	145	
		III	4.10 (1.92, 8.77)	126	
		IV	10.71 (4.72, 24.29)	50	
[b]Mayberry, et al. [1995][20]	Summary staging	I	1.0	185	Education, race, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, primary tumor status, node positivity, distant metastasis, and surgery.
		II	3.3 (1.70, 6.80)	315	
		III	8.6 (4.30, 17.00)	255	
		IV	52.7 (26.2, 105.8)	180	
		Unknown	7.7 (3.20, 18.70)	40	
[a]Robbins, et al. [2009][12]	Stage	I	1.00	14,971	Insurance status, age, facility type, neighborhood education level and neighborhood income level, and number of comorbidities.
		II	2.05 (1.77, 2.39)	15,194	
		III	3.71 (3.24, 4.24)	19,383	
		IV	21.51 (18.95, 24.42)	14,755	
Yan, et al. [2009][21]	SEER Stage (2 yrs since diagnosis)	I	1.00	1,481	Age, race, sex, marital status, socioeconomic status, tumor grade, and surgical treatment.
		II	2.35 (1.84, 2.99)	2,465	
		III	6.72 (5.33, 8.47)	1,903	
		IV	25.05 (19.8, 31.7)	2,101	
	SEER Stage (5 yrs since diagnosis)	I	1.00	1,481	Age, race, sex, marital status, socioeconomic status, tumor grade, and surgical treatment.
		II	1.84 (1.50, 2.25)	2,465	
		III	4.22 (3.48, 5.12)	1,903	
		IV	8.35 (6.33, 11.0)	2,101	

Table 2.19: continued

Study	Variable		Hazard Ratio for Mortality	Sample Size	Variables Adjusted for in Model
	SEER Stage	I	1.00	1,481	Age, race, sex, marital status, socioeconomic status,
	(10 yrs	II	1.22 (0.83, 1.79)	2,465	tumor grade, and surgical treatment.
	since	III	1.94 (1.30, 2.38)	1,903	
	diagnosis)	IV	1.34 (0.74, 2.43)	2,101	
[b]Jessup, et al.	AJCC	IIIA	1.00	4,085	Race, age, sex, histological grade, anatomic subsite,
[2005][28]	Cancer	IIIB	1.75 (1.65, 1.87)	25,900	surgery, and adjuvant chemotherapy.
	Substage	IIIC	2.95 (2.77, 3.14)	13,123	

Table 2.20: TNM Staging Components as Risk Factors for Colorectal and Colon Cancer Mortality among the White/NHW Population

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality	Sample Size	Variables Adjusted for in Model
Chatla, et al. [2005][27]	1	Stage: II	pT component of stage	pT3 pT4	1.00 6.37 (1.97, 20.60)	67 25	Age, gender, Bcl-2 expression, tumor location, tumor differentiation, and tumor size.
	2	Stage III	pT component of stage	pT3 pT4	1.00 0.56 (0.19, 1.60)	34 19	Age, gender, Bcl-2 expression, tumor location, tumor differentiation, and tumor size.
[a]Mayberry, et al. [1995][20]			Primary Tumor Status	T1 T2 T3 T4 Unknown	1.00 2.10 (0.7, 5.7) 8.00 (3.8, 17.1) 19.10 (8.5, 42.9) 19.20 (8.1, 45.5)	131 87 626 82 49	Education, race, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, node positivity, distant metastasis, and surgery.
Potosky, et al. [2002][23]			Tumor Extent	T1-T3 T4	1.00 1.80 (1.43, 2.25)	156 43	Standard therapy received, year of diagnosis, race, age at diagnosis, sex, SEER region, marital status, median income, cancer site, nodal status, histologic grade, and comorbidities.
Chatla, et al. [2005][27]	2	Stage III	pN component of stage	N1 N2-3	1.00 3.42 (1.37, 8.51)	41 25	Age, gender, Bcl-2 expression, pT component of stage, tumor location, tumor differentiation, and tumor size.

Table 2.20: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality	Sample Size	Variables Adjusted for in Model
Manne, et al. [1998][29]			pN component of stage	pN0	1.00	289	Age, gender, tumor location, tumor size, differentiation, pT component of stage, pM component of TNM stage, and nuclear accumulation of p53.
				pN1	1.79 (1.46, 2.18)	109	
				pN2	3.20 (2.14, 4.76)	68	
				pN3	5.72 (3.14, 10.40)	28	
[a]Mayberry, et al. [1995][20]			Node Positivity, N	0	1.00	470	Education, race, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, distant metastasis, and surgery.
				1-3	3.70 (2.7, 5.0)	240	
				>=4	6.80 (4.8, 9.6)	104	
				Unknown if <=3 or >=4	9.50 (5.9, 15.3)	35	
				Unknown	2.50 (1.7, 3.7)	126	
Potosky, et al. [2002][23]			Nodal Status	None or not stated	1.00	13	Standard therapy received, year of diagnosis, race, age at diagnosis, sex, SEER region, marital status, median income, cancer site, tumor extent, histologic grade, and comorbidities.
				1-3 Positive	1.06 (0.82, 1.38)	119	
				>=4 Positive	2.05 (1.56, 2.69)	68	
[a]Mayberry, et al.[20] [1995]			Distant Metastasis	No	1.00	781	Education, race, poverty index, type of insurance, number of comorbid conditions, bowel obstruction, anatomic site, grade, histology, nuclear atypia, summary staging, primary tumor status, node positivity, and surgery.
				Yes	12.40 (9.6, 15.8)	180	

Table 2.20: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality	Sample Size	Variables Adjusted for in Model
Manne, et al. [1998][29]			M component of stage	M0 M1	1.00 4.44 (2.62, 7.53)	424 80	Age, gender, tumor location, tumor size, differentiation, pT component of stage, pN component of stage, and nuclear accumulation of p53.

comparisons, they suggest that an increase in the N component increases risk for CRC and colon cancer mortality.[20,23,27,29] According to Chatla[27], *et al*. Stage III cases having N2-N3 increased ones CRC risk to 3.42 times higher than being at a N1.[27]

The Metastases component (M0-M1) has also been independently examined to see if this factor influences mortality risk. Individuals who were diagnosed with distant metastases (M1) had a high risk for CRC and colon cancer mortality ranging from 4.44 to 12.4 times higher than those without distant metastases (M0).[20,29]

Genetic Factors

Genetic components have also been investigated for their affect on risk for mortality among the White population (Table 2.21). The Bcl-2 protein plays a role in tumor progression and abnormal expression of this protein has been suggested to cause cancer. At Stage II, those with a low Bcl-2 expression had 8.48 times higher risk for CRC mortality than those with high Bcl-2 expression.[27] Stage III findings were not statistically significant, but there may be an increased risk for CRC mortality for those with low Bcl-2 expression.[27] Patients with distal adenocarcinoma and p53 accumulation results were not statistically significant (HR=2.06, CI=0.97-4.35).

It has been found that having a mutated p53 gene promotes tumor progression. A mutated p53 gene has a 1.55 times higher risk of CRC mortality than not having a mutated p53 gene.[31] Patients with proximal tumors that had nuclear p53 accumulation were 6.77 times more likely to die than patients who were negative for p53 accumulation.[29]

The Pro/Pro variant of the codon 72 polymorphism has an increased potential for cancer cell proliferation. Although the results are not statistically significant, there is

Table 2.21: Genetic Characteristics to Predict Risk for Colorectal Cancer Mortality for the White/NHW Population

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality	Sample Size	Variables Adjusted for in Model
Jones, et al. [2009][25]			GSTM1	Wild Type	1.00	112	Age, race, gender, TNM stage at diagnosis, self-rated health, smoking status, and receipt of chemotherapy.
				Null	1.31 (0.85, 2.00)	79	
			GSTT1	Wild Type	1.00	166	Age, race, gender, TNM stage at diagnosis, self-rated health, smoking status, and receipt of chemotherapy.
				Null	1.44 (0.85, 2.44)	30	
			GSTP1	Wild type (lle/lle)	1.00	92	Age, race, gender, TNM stage at diagnosis, self-rated health, smoking status, and receipt of chemotherapy.
				lle/Val	0.81 (0.52, 1.30)	63	
				Val/Val	0.55 (0.31-0.99)	38	
				lle/Val or ValVal	0.72 (0.48, 1.09)	101	
Chatla, et al. [2005][27]	1	Stage: II	Bcl-2 expression	High	1.00	57	Age, gender, pT component of stage, tumor location, tumor differentiation, and tumor size.
				Low	8.48 (2.29, 31.45)	35	
	2	Stage: III	Bcl-2 expression	High	1.00	32	Age, gender, pN component of stage, pT component of stage, tumor location, tumor differentiation, and tumor size.
				Low	1.52 (0.60-3.88)	34	
Katkoori, et al. [2009][31]			p53 Status	Wild Type	1.00	178	Age, gender, tumor location, tumor stage, tumor size, and codon 72 polymorphism.
				Mutated	1.55 (1.04, 2.32)	195	

Table 2.21: continued

Study	Model	Stratification Variable	Variable		Hazard Ratio for Mortality	Sample Size	Variables Adjusted for in Model
			Codon 72 polymorphism	Arg/Arg or Arg/Pro	1.00	332	
				Pro/Pro	1.60 (0.69, 3.18)	41	
Manne, et al. [1998][29]			Nuclear Accumulation of p53	Proximal Colon			Age, gender, tumor location, tumor size, differentiation, pT component of stage, pN component of stage, and pM component of TNM stage.
				$p53^-$	1.00	126	
				$p53^+$	6.77 (3.08, 14.87)	89	
				Distal Colorectum			
				$p53^-$	1.00	116	
				$p53^+$	2.06 (0.97, 4.35)	173	

potentially increased risk for CRC mortality for the Pro/Pro variant, in comparison to having the Arg/Arg or Arg/Pro variant of the codon 72 polymorphism (HR-1.60, CI=0.69-3.18).[31]

Discussion

This review clearly uncovered a disparity in colorectal cancer research between AI/AN and Whites/NHW. The only risk factor explored among AI/AN is race, whereas among Whites/NHW, there has been a number of areas explored (Figure 2.1). In order to effectively increase survival outcomes among AI/AN, it is essential to understand the risk factors that contribute to mortality. Therefore, recommendations for future colorectal cancer research among AI/AN needs epidemiological exploration in the areas of tumor biology/genetics, health system, lifestyle, treatment, and demographic and clinical factors.

This study systematically reviewed a number of important, significant risk factors for mortality. However, it did not retrieve other known or suspected risk factors, including: body anthropometrics (height and body mass index), diet/nutrition (alcohol consumption, meat consumption), factors that impact treatment (transportation, access to treatment, social support, functional status, cognitive status, and cancer knowledge), prevention (colorectal cancer screening), access to treatment, and other factors (physical activity, use of NSAIDS, and family history).

In this review, we found limited but suggestive evidence for geographic differences in mortality.[13,23] Knowing that incidence rates vary by region for the AI/AN population, one could hypothesize that risk for mortality may also be diverse for this regionally fragmented population.

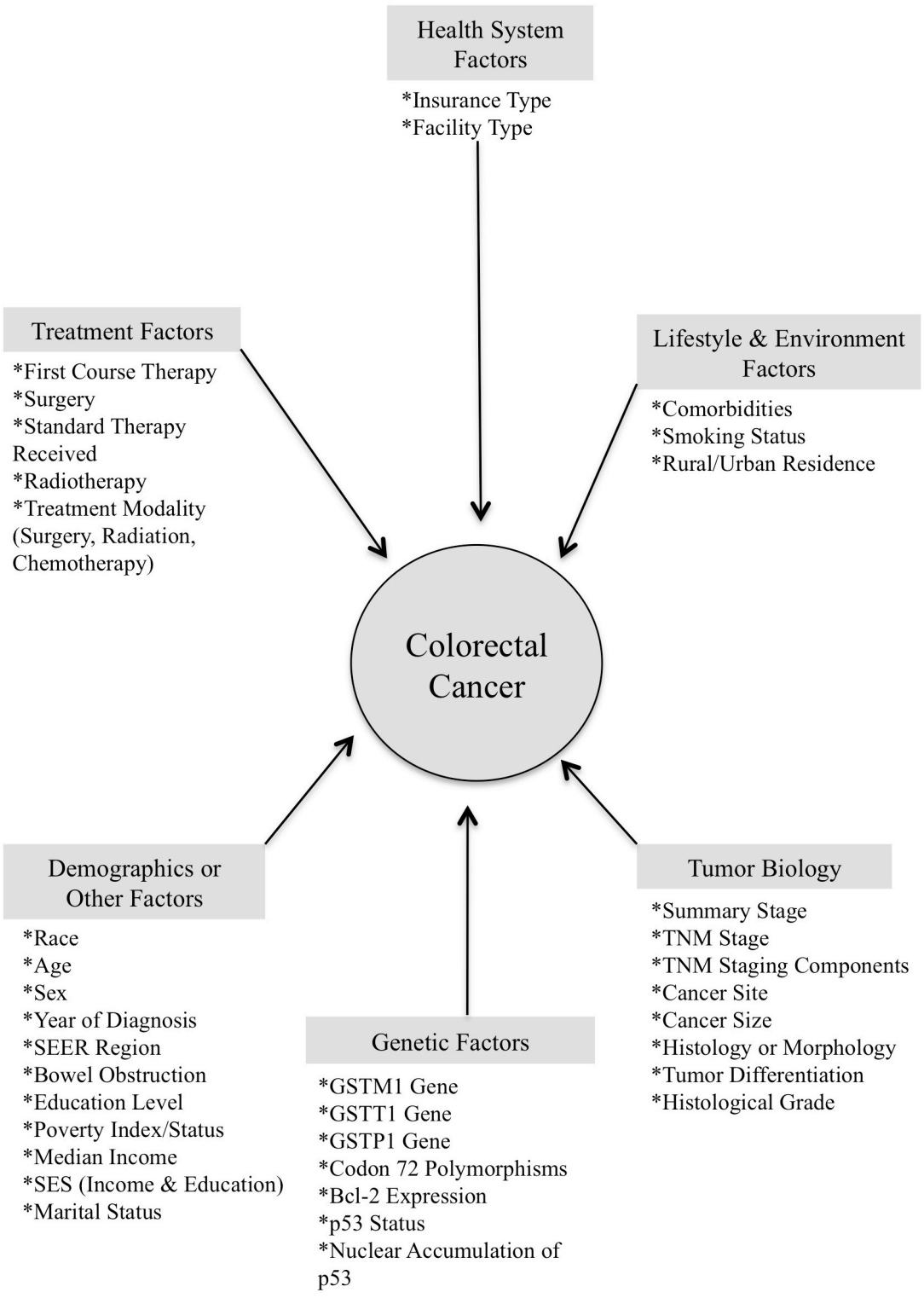

Figure 2.1: Risk Factors Found in Colorectal Cancer Survivorship among White/NHW

Another important factor that may impact risk for mortality is access to CRC screening and treatment. A review examining urban/rural residency[13] and often urban/rural residency is used as a proxy for access to care. Research examining access to screening and treatment in AI/AN population is surely needed. This study examines how distance to CRC screening and treatment affects risk for mortality for AI/AN and NHW.

The disparity in colorectal cancer research is unfortunate, but not surprising. Epidemiological cancer research among the AI/AN population is a difficult task because many of the statistical tests require large populations for analyses. In order to examine multiple risk factors for survival or mortality among AI/AN, investigators must obtain data from population-based cancer registries to achieve enough power to detect significant differences.

Clinical data among the AI/AN population are also essential; however, there are a number of issues associated with the collection of data from AI/AN. First, the small population size of AI/AN forces investigators to wait several years in order for the sample to reach sufficient size for analysis. Second, the various risk factor data must be obtained, including lifestyle or behavioral factors, which are not routinely collected by central registries. Third, working with AI/AN is challenging as communities are not typically located in urban centers where most cancer treatment facilities are located and the negative experiences with research historically, which has lead to growing mistrust and apprehension to participate in research.

An alternative to primary data collection is the utilization of cancer registry and administrative health data such as Medicare. The SEER-Medicare linked database contains both tumor registry information and enrollment and claims data. It has been

available since 1991, but has not been fully utilized to examine cancer issues among AI/AN populations.

Utilizing SEER-Medicare data, geographic measures of urban/rural, distance to treatment and screening, and comorbidities will be investigated to determine their association with CRC mortality among AI/AN and NHW.

Another important factor that may impact risk for mortality is access to CRC screening and treatment. One study in the review examined urban/rural residency[13] and often urban/rural residency is used as a proxy for access to care. Much needed is an examination of access to screening and treatment but with a measure that is more precise than urban/rural residence. The next goal of the author will be to examine how distance to CRC screening and treatment affects risk for mortality.

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CHAPTER 3

THE IMPACT OF COMORBIDITY ON COLON CANCER MORTALITY AMONG AMERICAN INDIANS/ALASKA NATIVES AND NON-HISPANIC WHITES

Abstract

Comorbidity are theorized to impede cancer treatment plans, increase complications, decrease access to care, and can negatively impact survival. The impact of comorbidity on colon cancer (or colorectal cancer) mortality has been examined with a variety of measures and with contrasting results. When examining whether American Indians/Alaska Natives (AI/AN), in comparison to Whites, had an increased risk for colon cancer or colorectal cancer (CRC) mortality, past studies also had varying results.

This retrospective cohort study examines the impact of comorbidity and race on colon cancer mortality. The AI/AN (n=490) and Non-Hispanic White (NHW; n=137,877) cancer cases came from the 1991-2007 SEER-Medicare linked database. Stratified by race, cox proportional hazards regression was utilized to determine risk factors for colon cancer mortality while controlling for demographic, diagnostic, and socioeconomic factors.

Among NHW, the Charlson Comorbidity Index (CCI) demonstrated, as the CCI increased, risk for colon cancer mortality increased. A CCI of 1 had a 1.36 (CI 1.31-1.40) times increased risk, a CCI of 2 had a 1.66 (CI 1.57-1.75) times increased risk, and a CCI

of 3 or more had a 2.23 (CI 2.09-2.38) times increased risk for colon cancer mortality. Race was an additional risk factor examined. In comparison to NHW, the data suggest that AI/AN have an increased risk for colon cancer mortality but results were not significant (H.R.=1.07, CI 0.89-1.28).

Comorbidity impact colon cancer mortality. AI/AN appear to have an increased risk for colon cancer mortality but the results were not significant. There is limited information regarding risk factors for the AI/AN population and this needs to be explored further.

Introduction

Comorbidity is a disease or multiple diseases existing concurrently but independently with the primary disease of interest. Comorbidity are viewed as problematic with cancer care because comorbid conditions may impede cancer treatment plans, increase the chances of complications, and limit access to care and thus, negatively impact survival.[1-3]

It has been found that patients with comorbidity are less likely to receive treatment consistent with guidelines and experience unplanned delays in treatment initiation.[3] When looking at specific types of treatment, studies have found that patients with comorbidity are less likely to complete, receive, and/or initiate chemotherapy.[3,4] An additional study found that oncologists recommend adjuvant chemotherapy for healthy, 55-year old patients with stage III colon cancer but were less likely to recommend chemotherapy for younger or older patients with any comorbidity.[5] There are also differences in radiation therapy among cancer patients with comorbidity and without. Patients with low or moderate but not severe comorbidity are more likely to experience

delays in radiation therapy initiation and patients with comorbidity are more likely to receive radiation therapy after a delay and less likely to receive a complete radiation therapy course.[3] There are differing results regarding CRC patients undergoing surgery and whether comorbidity may impede surgery outcomes.[4,6-8] Patients with significant comorbidity have been denied laparoscopic CRC resections[9] and are more likely to experience complications after surgery.[3] These patients are also less likely to be referred to a medical oncologist.[3]

The impact of comorbidity on colon cancer or CRC mortality has been examined with innovated measures and the results have been variable. Studies that summed comorbidity found a slight increase for either colon cancer or CRC mortality for those who had comorbidites.[10,11] However, the Gomez study had significant results while the Mayberry study did not.[10,11]

Other studies used various comorbidity indices to determine its impact on colon, CRC, or all-cause mortality. Studies that used either the Elixhauser Index or the Charlson-Deyo index established an increase in index also increases one's risk for all-cause mortality for CRC patients.[12,13] Research using the Charlson Comorbidity Index (CCI) found an increase in index also increases one's risk for colon cancer or CRC mortality but the results were nonsignificant.[14,15]

Regarding race, past studies had varying results when examining whether AI/AN had increased risk for all-cause, colon, or CRC cancer mortality.[16-19] AI/AN demonstrated an increased risk for all-cause and CRC mortality but the results were not significant.[16,19] Two studies found greater risk for CRC cancer mortality among female AI/AN than female NHW.[17,18] Other studies found increased risk for CRC cancer for men and women

but the results were not significant.[16-19] Risk for cancer survival may be ambiguous, but when examining life expectancy, rates per 100,000 are lower for American Indians/Alaska Natives (73.6) than Whites (77.7).[20] With race being a debatable risk factor for cancer survival, this study will also examine whether race is a risk factor for colon cancer survival.

This study utilizes the CCI to determine the impact of comorbidity on colon cancer mortality among AI/AN and NHW. The impact of race (AI/AN versus NHW) on colon cancer mortality will also be examined.

Data and Methods

Design and Data Sources

This study was a retrospective cohort study that examined the impact of comorbidity and race for colon cancer mortality among AI/AN and NHW. Data were acquired from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, which is composed of the Patient Entitlement and Diagnosis Summary File (PEDSF), Medicare Provider Analysis and Review (MEDPAR), Carrier Claims (NCH), and Outpatient Claims (OUTPAT) databases. The PEDSF (1991-2007) contains the cancer information on diagnosed cancer cases from people residing in various SEER regions. These regions included the states of Connecticut, Hawaii, Iowa, New Mexico, California, Kentucky, Louisiana, New Jersey, Georgia, and Utah and metropolitan areas of Detroit and Seattle-Puget Sound. Alaska and Arizona are not included in the linked database. The remaining files (MEDPAR, NCH, and OUTPAT) contain various types of Medicare claims data from 1991 to 2008.

Study Population

Colon cancer cases came from the SEER-Medicare linked database. Inclusion criteria included all ages, cancer diagnosed from 1991-2007, race (AI/AN and NHW), single primary of CRC cases, death not determined by autopsy or death certificate, and solely colon cases. Exclusion criteria were missing survival years and missing stage at diagnosis. The final sample size was a total of 138,367 participants with 137,877 being NHW and 490 being AI/AN. See Figure 3.1 for a visual of the sampling scheme.

Description of Variables

Survival Years

Survival years for colon cancer were calculated in months from the date of diagnosis to the date of colon cancer death. The SEER date of diagnosis was used. Censored individuals were those who were alive at follow-up (December 31, 2009) and also those who died from other causes, except colon cancer.

Comorbidity Index

The CCI was used in this study.[21] Comorbidity were extracted from the Medicare claims files (MEDPAR, NCH and OUTPAT) utilizing the SAS macro that was developed by SEER. The window of time to capture comorbidity is one year prior to diagnosis through the month of diagnosis. The macro created weighted comorbidity scores based on severity of disease and combination of diseases.

Statistical Analysis

Bivariate analyses (Mann-Whitney and Chi-square tests) were used to determine if there are any differences between AI/AN and NHW. Chi square test, with an alpha

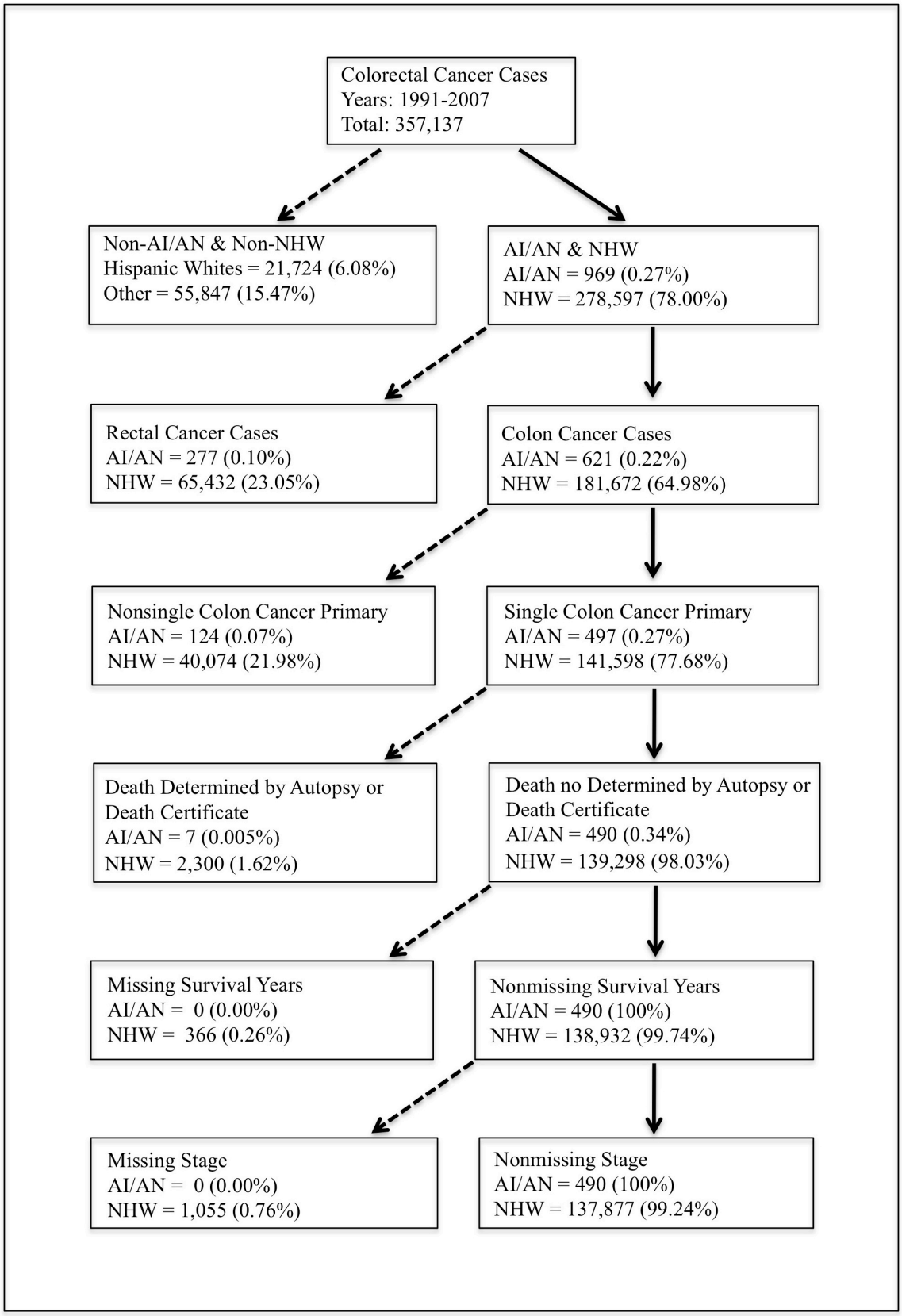

Figure 3.1: Sampling Flow Chart of the Study Population.

level of 0.007, was used to determine if differences had statistical significance between the races. The alpha level was corrected using Bonferroni's correction using 7 comparisons. Cox proportional hazards regression was utilized to determine risk factors for colon cancer mortality, while adjusting for demographics, diagnostic, and socioeconomic factors. SAS statistical software, version 9.2, was used for data management and to conduct the analyses (SAS Institute Inc., Cary, NC).

Results

Bivariate analyses (Chi-square test, t-test, and Mann-Whitney-Wilcoxon test) were conducted to determine if there were any differences in demographic and clinical characteristics between AI/AN and NHW (Table 3.1). More AI/AN were diagnosed with colon cancer at a younger age. More AI/AN (34.69%) were 65 and younger than NHW (19.19%). AI/AN were also more likely to be single/separated/divorced (21.22%) compared to NHW (14.98%) but less AI/AN (23.88%) were widowed compared to NHW (28.96%). The median census tract income for AI/AN ($34,890) was lower than NHW ($47,533). In order to qualify for Medicare, one must either age into the system when they turn 65 or if they have a disability or end stage renal disease, they qualify for Medicare. There were more AI/AN (24.90%) that entered the system being disabled or having end stage renal disease than NHW (10.67%).

The main analyses were Cox proportional hazard regression models examining whether race and comorbidity impact colon cancer mortality after controlling for stage at diagnosis, age at diagnosis, sex, census tract income, and marital status at diagnosis (Table 3.2). Examining model 1, which is the model that includes both AI/AN and NHW, the results for race were not significant. However, model 1 suggests that AI/AN have a

Table 3.1: Bivariate Analyses of the Characteristics of Colon Cancer Patients by Race.

Variable	AI/AN N= 490 No. (%)	NHW N= 137,877 No. (%)	P Value
Age at Diagnosis			
<=65	170 (34.69)	26,459 (19.19)	<0.0001
>65	320 (65.31)	111,418 (80.81)	
Mean Age at Diagnosis (Range)	69.27 (28-98)	74.43 (21-108)	<0.0001
Sex			
Male	220 (44.90)	63,271 (45.89)	0.6602
Female	270 (55.10)	74,606 (54.11)	
Marital Status			
Single/Separate/Divorced	104 (21.22)	20,654 (14.98)	<0.0001
Married	233 (47.55)	71,811 (52.08)	
Widowed	117 (23.88)	39,927 (28.96)	
Unknown	36 (07.35)	5,485 (03.98)	
Census Tract Income			
Median Income[1] (Range)	34,890 (12,507-115,434)	47,533 (7-200,008)	<0.0001
Reason for Entitlement			
Age	368 (75.10)	123,149 (89.33)	<0.0001
Disability or End Stage Renal Disease	122 (24.90)	14,706 (10.67)	
Cancer Stage			
Early	176 (35.92)	56,589 (41.04)	0.0159
Late	297 (60.61)	74,829 (54.27)	
Unstaged	17 (03.47)	6,459 (04.68)	
Cause of Death			
Alive	241 (49.18)	65,149 (47.25)	0.1330
Colon Death	143 (29.18)	38,355 (27.82)	
Other Cancer Death	20 (04.08)	4,480 (03.25)	
Other Cause of Death	86 (17.55)	29,893 (21.68)	
Median Survival Years (Range)	2.16 (0-17.01)	2.67 (0-17.01)	0.0471

[1] Wilcoxon Test, two-sided (z= -18.7972)

Table 3.1: continued

Variable		AI/AN N= 302 No. (%)	NHW N= 94,146 No. (%)	P Value
Mean Survival Years (Range)		3.65 (0-17.01)	3.90 (0-17.01)	0.1663
Charlson Comorbidity Index[2]		383 (78.16)	112,652 (81.70)	0.1133
	0	61 (12.45)	15,854 (11.50)	
	1	28 (05.71)	5,632 (04.08)	
	2	18 (03.67)	3,739 (02.71)	
	3+			

[2] Window of time is 1 year prior to diagnosis through the month of diagnosis.

Table 3.2: Multivariate Cox Proportional Hazards Regression of Risk Factors Associated with Colon Cancer Mortality among AI/AN and NHW.

	Model 1 AI/AN & NHW N=138,367 D=39,584		Model 2 AI/AN N=490 D=143		Model 3 NHW N=137,877 D=38,355	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Cancer Stage						
Early	Ref	Ref	Ref	Ref	Ref	Ref
Late	1.60 (1.56-1.63)	<0.0001	1.36 (0.91-2.01)	0.1310	1.60 (1.56-1.63)	<0.0001
Unstaged	2.36 (2.24-2.49)	<0.0001	2.66 (1.02-6.96)	0.0457	2.39 (2.24-2.49)	<0.0001
Age at Diagnosis	1.03 (1.03-1.03)	<0.0001	1.02 (1.00-1.03)	0.1221	1.03 (1.03-1.03)	<0.0001
Sex						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.15 (1.13-1.18)	<0.0001	1.06 (0.71-1.58)	0.7733	1.15 (1.13-1.18)	<0.0001
Income	0.99 (0.98-0.99)	<0.0001	0.98 (0.85-1.13)	0.7417	0.99 (0.98-0.99)	<0.0001
Marital Status						
Single[3]	1.20 (1.16-1.24)	<0.0001	1.34 (0.81-2.22)	0.2510	1.20 (1.16-1.24)	<0.0001
Married	ref	ref	ref	ref	ref	ref
Widowed	1.09 (1.06-1.12)	<0.0001	1.23 (0.73-2.10)	0.4380	1.09 (1.06-1.12)	<0.0001
Unknown	1.04 (0.99-1.10)	0.1455	1.52 (0.78-2.98)	0.2229	1.04 (0.98-1.10)	0.1723
Race						
NHW	Ref	Ref				
AI/AN	1.07 (0.89-1.28)	0.4975				
CCI						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.35 (1.31-1.40)	<0.0001	1.00 (0.52-1.95)	0.9944	1.36 (1.31-1.40)	<0.0001
2	1.65 (1.56-1.75)	<0.0001	1.07 (0.48-2.41)	0.8653	1.66 (1.57-1.75)	<0.0001
3+	2.23 (2.09-2.39)	<0.0001	2.46 (0.98-6.17)	0.0559	2.23 (2.09-2.38)	<0.0001

[3] Single, separated, or divorced

higher risk for colon cancer mortality than NHW (H.R.=1.07, CI 0.89-1.28). The CCI demonstrated that as one's CCI increased, their risk for colon cancer mortality increases. A CCI of 1 had a 1.35 (CI 1.31-1.40) times increased risk, a CCI of 2 had a 1.65 (CI 1.56-1.75) times increased risk, and a CCI of 3 or more had a 2.23 (CI 2.09-2.39) times increased risk for colon cancer mortality.

A separate model was built for NHW but since the population is quite large in comparison to AI/AN, the results mimic model 1, which combines both races in the model. The comorbidity index for the AI/AN population has a similar risk trend as model 1 and 2 in Table 3.2, but the results were not signification (Table 3.2, model 2).

Discussion

The impact of comorbidity on colon cancer mortality was examined and results demonstrated that as CCI increases, one's risk for a colon cancer death also increases. Two other studies examined the affect of the increase in a CCI on CRC and colon cancer mortality and found similar results but their findings were statistically nonsignificant.[14,15] These nonsignificant results may have been due to a small sample sizes.

The study population is a Medicare population that has had colon cancer and they do not represent the general population. This population has health care coverage through Medicare, whereas in the general population, not all AI/AN or NHW have health insurance coverage. A proportion of the population (10.13%) has end-stage renal disease and/or a disability. All ages were included in the study population, but this study population is an older population than the general United States population.

The results demonstrate there is an association between comorbidity and colon cancer mortality, but by what means are comorbidity affecting colon cancer mortality? It

has been suggested that comorbid conditions could negatively impact treatment plans, increase complications, and decrease access to care.[1-9] Further investigation is needed to understand how comorbidity impact mortality outcomes.

This study has limitations. The comorbidity measure may be underestimated. Comorbidity were determined by examining the month of diagnosis and 12 months prior to date of diagnosis and approximately 16.64% of the study population does not have a full year of coverage, which means they do not have a complete year of claims to examine. There may also be additional underestimation because not all preexisting secondary diagnoses are noted in the medical record, thus, they are not in the claims. Furthermore, some comorbid conditions may be underreported in the claims record.[22] The underestimation of comorbidity may have calculated lower comorbidity scores. The underestimation of comorbidity scores may also give an underestimation of risk for colon cancer mortality.

The AI/AN sample is quite small and thus the study could not examine if there are racial differences in terms of survival. Although the 1.3 hazard ratio for the AI/AN race was not significant, it does suggest that there are other risk factors that may be associated with the AI/AN population which are impacting a higher risk for a colon cancer death in this population. The lack of sample size for the AI/AN population is an issue and will continue to be an issue because of the exclusion of AI/AN from Arizona and Alaska. However, it can be suggested, from the main effects model (Table 3.2, model 1), that an increased CCI is also an issue for the AI/AN population.

Conclusion

Comorbidity increases one risk for colon cancer mortality and need to be assessed as a risk factor. However, the process of how comorbidity impact colon cancer mortality is not fully understood and needs to be examined more thoroughly. The process may be different for various groups. For instance, race, gender, geographic residence, and other groups may have differential impact; the impact may be treatment plans, increase chances of complications, or less access to care.

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CHAPTER 4

THE IMPACT OF GEOGRAPHIC BASED ACCESS ON COLON CANCER SURVIVAL AMONG AMERICAN INDIANS/ALASKA NATIVES AND NON-HISPANIC WHITES

Abstract

Risk factors for colon cancer mortality have been studied more thoroughly in the White or non-Hispanic White (NHW) population, compared to the American Indian/Alaska Native (AI/AN). Race (AI/AN) as a risk factor has been the only factor examined for colon (or colorectal) cancer mortality. Results have shown an increased risk for AI/AN, but statistical significance has not been consistent. Geographic access using rural/urban measures have also been examined but with varying results. To a lesser extent, travel time to treatment and screening and their impact on colon cancer mortality has been explored and results have been inconclusive or nonsignificant.

This retrospective cohort study examines how travel time to treatment and screening impacts colon cancer mortality among AI/AN and NHW. The study uses colon cancer cases from the SEER-Medicare linked database (1991-2007). Geographic Information System methodology was used to calculate travel times. Cox proportional hazards regression was utilized to determine risk for colon cancer mortality.

The study found that NHW traveling 60 minutes or more to a colonoscopy or sigmoidoscopy screening facility, compared to living <30 minutes away, indicated

increased risk for colon cancer mortality (HR=1.56, CI 1.16-2.09). AI/AN living 60 minutes or more from a chemotherapy center had an increased risk for colon cancer mortality compared to AI/AN living <30 minutes (HR= 2.57, CI 1.39-4.76). For NHW colon cancer patients at all stages, traveling 60 minutes or more had an increased risk for colon cancer mortality (HR=1.59, CI 1.18-2.13) than those living <30 minutes away. NHW living 60 minutes or more, rather than <30 minutes, to a surgical facility demonstrated slightly less risk for colon cancer mortality (HR=0.92, CI 0.85-0.99).

Travel times, rather than rural/urban measures, appears to capture risk better for colon cancer mortality. Travel time to screening is the biggest factor in reducing colon cancer mortality and screening should target those having to travel further distances. Lower risk for colon cancer mortality for those living further from a surgical center needs to be explored for reasons why this is the case. For the AI/AN population, having access to chemotherapy appears to impact colon cancer mortality and transportation or increased chemotherapy facilities may help create better access. Although travel time to screening for the AI/AN population is not significant, the data suggest that traveling more than 30 minutes may be a barrier for the AI/AN population.

Introduction

Risk for colon cancer mortality has been studied more thoroughly in the White or non-Hispanic White (NHW) population, in comparison to the American Indian/Alaska Native (AI/AN) population. There have been a number of studies that have examined risk factors for colon cancer or colorectal cancer (CRC) mortality among NHW and have found demographic, clinical, lifestyle, health system, treatment, tumor biology, and genetic factors are associated with colon cancer mortality.[1-18] When examining the

AI/AN studies for risk of colon cancer or CRC mortality, race was the main predictor explored, after controlling for various factors. These studies suggest that risk for mortality is higher among AI/AN than NHW.[19-22] However, the results from these studies had statistically significant discrepancies.

Geographic predictors have also been examined using dichomotous measures and travel times to determine their affect on colon cancer or CRC survival. Rurality and urbanicity have been explored as a predictor for obtaining surgery,[23,24] radiation, and chemotherapy with results suggesting that rural residents are less likely to obtain treatment.[23,24,25] A problem with a rural/urban measure is that it can be a proxy for other measures. For instance, rural/urban could potentially be measuring income, education, travel time/distance, transportation, or all these measures and more.

Travel time to treatment would be a more precise measure to determine its impact on colon cancer or CRC survival rather than a rural/urban measure. Two studies found travel time to radiation increases risk for death.[26,27] However, another study did not find that increased travel impacted the odds of obtaining radiation and surgery.[24] Travel time to CRC treatment and its affect on survival has mainly been explored in other countries,[26-29] with one study in the United States.[30] This study examines the impact of race and travel time to treatment and screening on colon cancer survival among AI/AN and NHW patients.

Data and Methods

Data Sources

Colon cancer cases were identified in the Surveillance, Epidemiology and End Results Program (SEER)-Medicare linked database from 1991-2007. The SEER-

Medicare linked database obtains cancer cases from the following geographic areas: San Francisco/Oakland, Detroit, Seattle, Atlanta, rural Georgia, California, Connecticut, Iowa, New Mexico, Utah, Hawaii, Kentucky, Louisiana, and New Jersey. The SEER-Medicare linked database is made up of various files; this study used the Patient Entitlement and Diagnosis Summary File (PEDSF), Medicare Provider Analysis and Review (MEDPAR), Carrier Claims (NCH), and the Outpatient File (OUTPAT). The 1991-2008 Provider of Services (POS) files from Medicare were also utilized.

Study Population

The population consisted of 94,448 people: 94,146 were NHW and 302 were AI/AN. Inclusion criteria were first diagnosis of colon or rectal cancer, diagnosed during the 1991-2007 time period, death not determined by autopsy or death certificate, and they had to be NHW and AI/AN. Exclusion criteria were if they were missing any of the distances to treatment and screening centers, had missing survival years, missing stage at diagnosis, and missing geographic residence at diagnosis (rural/urban). Figure 4.1 gives an overview of the exclusion/inclusion criteria.

Description of Variables

Mortality

Colon cancer mortality was calculated in months from the date of diagnosis to the date of colon cancer death using the SEER-defined date of diagnosis and date of colon cancer death. Those who remained alive at last follow-up (December 31, 2009) and who died from other causes were censored.

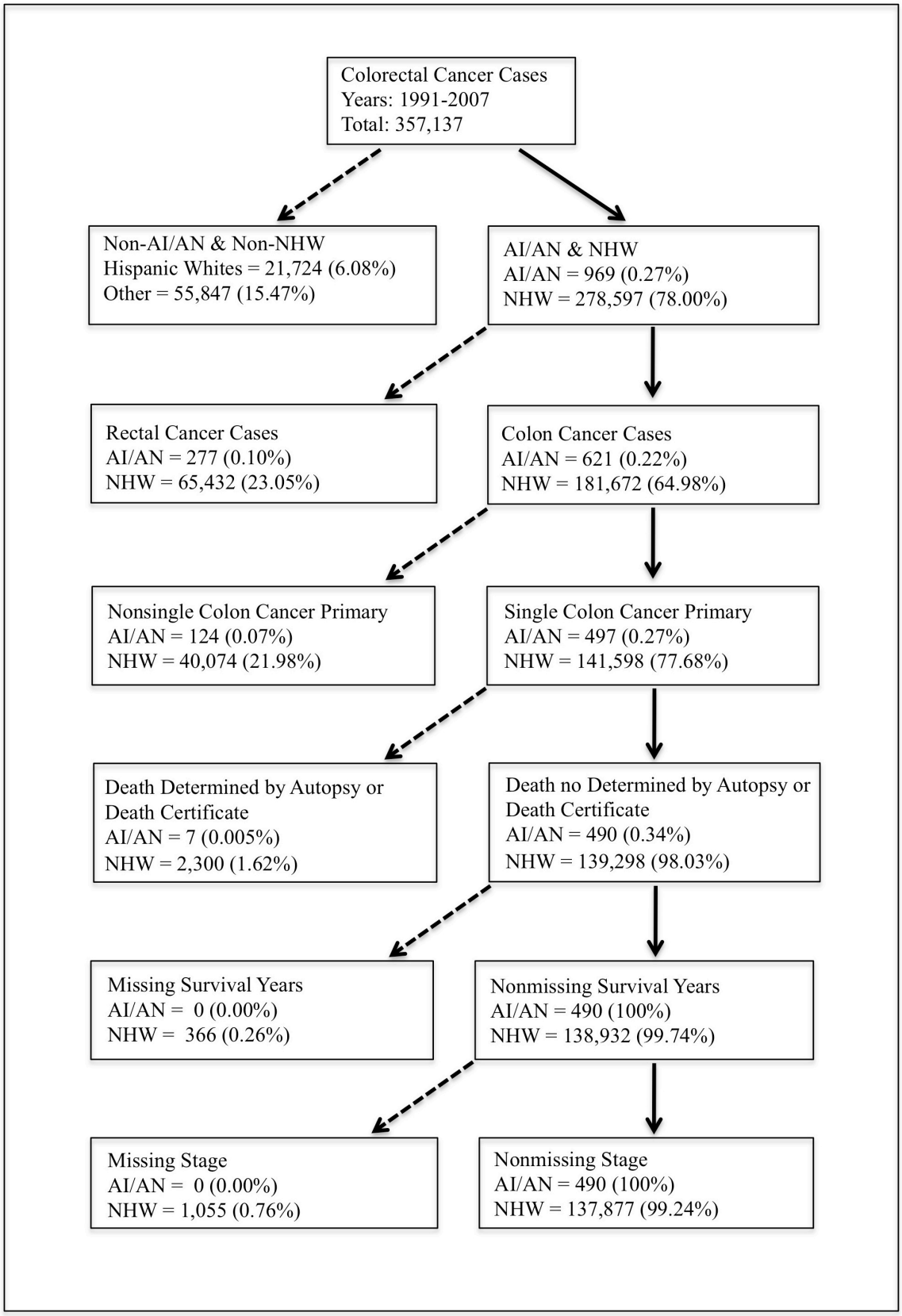

Figure 4.1: Sampling Flow Chart of the Study Population.

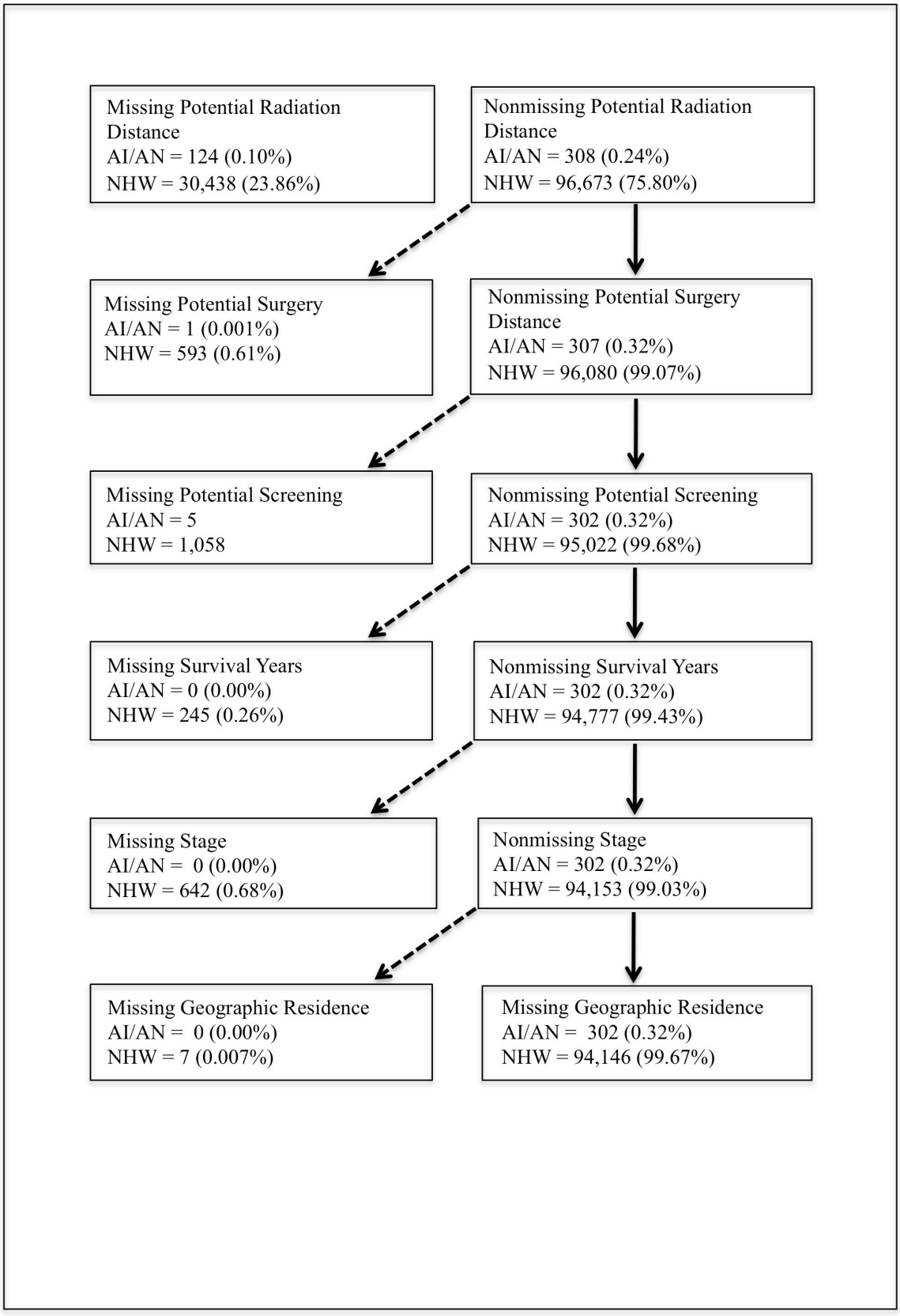

Figure 4.1: continued

Rural/Urban

Rurality and urbanicity were developed using the Rural Urban Continuum Codes (RUCC). These codes are available in the PEDSF. The 9 RUCC were collapsed into metropolitan/urban and nonmetropolitan/rural. Codes 1-3 were used for urban and codes 4-9 for rural.

Travel Time to Treatment

In order to compare results to other studies, travel time was used rather than distance. Three measures were developed for travel time to treatment: (1) travel time to chemotherapy facility, (2) travel time to radiation facility, and (3) travel time to surgical facility.

Providers' zip code areas came from the NCH file. Treatment information came from the NCH file. International Classification of Diseases (ICD)-9-CM codes, Healthcare Common Procedure Coding System (HCPCS) codes, and Current Procedural Terminology (CPT) codes for chemotherapy, radiation, and surgery from 1991-2007 were used to determine if an individual had chemotherapy, radiation, and/or surgery. (A list of the codes can be found in Appendix A.) Once treatment information was determined, the corresponding chemotherapy, radiation, and surgery zip codes were obtained from the NCH data. Zip code areas were mapped; one map for each treatment type. Providers' addresses from the POS file were geocoded within each zip code area to provide a point for each treatment type.

Patients' census tracts came from the PEDSF and these were mapped on each type of treatment map. Census tract centroids were determined using 1990 and 2010 American Indian (AI) census and White populations. Ten driving times from centroids to the closest

addresses were calculated using ESRI ArcGIS software (version 10.1) and StreetMap Premium for ArcGIS. Median travel times were calculated using travel times to facilities that were in existence during patients' year of diagnosis.

To illustrate travel times development, see Figure 4.2. Travel times were calculated between a patient's census tract centroid and up to 10 closest travel times. As an example, suppose D2, D6, and D8 treatment facilities were not in existence during the patient's cancer diagnosis. The calculations of median travels would use the travels times of D1, D3, D4, D5, D7, D9, and D10 in the calculation.

Travel Time to Potential Screening

Travel times for potential screening (colonoscopy or sigmoidoscopy) were calculated in a similar manner. Addresses for Medicare screening facilities were unavailable, so treatment addresses were used as a proxy for screening facilities. Providers' zip code areas were determined in the same manner as above, but screening billing codes were used instead of treatment codes. These codes can be found in Appendix B. The final variable for screening used the closest travel time for either a colonoscopy or sigmoidoscopy travels times.

Statistical Analysis

The data were analyzed using SAS 9.2 (SAS Institute Inc, Carry, NC, 2001). Bivariate analyses were used to assess statistical differences between AI/AN and NHW for the demographic, clinical characteristics, and geographic measures. Multiple comparisons were conducted. Hence, significance was adjusted using Bonferroni's correction. Cox proportional hazards regression was used to estimate relative risk for

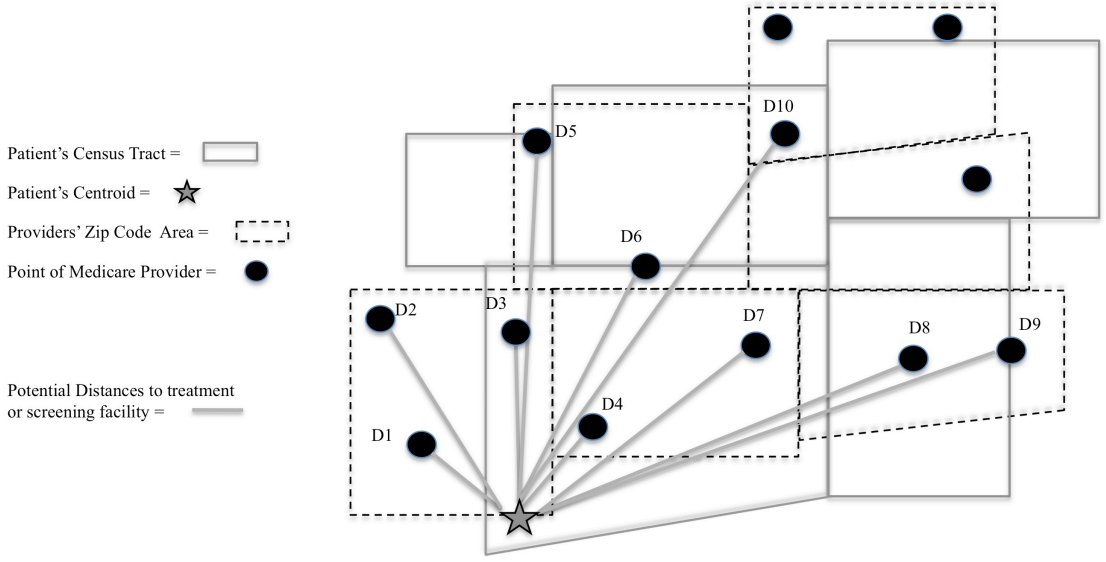

Figure 4.2: Diagram of Potential Travel Times to Treatment or Screening Facilities.

colon cancer mortality.

Results

Three main analyses were conducted for this study. First, bivariate analyses (Chi-square test, T-test, or Mann-Whitney-Wilcoxon test) of demographic, socioeconomic, and clinical characteristics were used to determine if there were any differences between AI/AN and NHW. The second analysis examined the impact of travel times to treatment and screening on colon cancer mortality using cox proportional hazards modeling. Third was the examination of the effect of travel times to treatment and screening based on the appropriate care by cancer stage(s) utilizing cox proportional hazards regression.

Demographic and Clinical Comparisons

Bivariate analyses for demographic, socioeconomic, clinical characteristics, and travel times for colon cancer patients can be found in Table 4.1. The mean age at diagnosis was younger for AI/AN (69.88%) patients than NHW (74.44%) patients. (Mean age was the same as the median age.) More AI/AN (21.52%) were single or separated or divorced than NHW (14.62%). NHW (52.29%) were more likely to be married than AI/AN (44.04%) and more NHW (29.08%) were widowed than AI/AN (26.49%). Median census tract income for AI/AN patients ($35,428) was lower than NHW patients ($47,288).

In order to qualify for Medicare, one must qualify by age (65 or above) or have a disability and/or end stage renal disease. There were more NHW patients (89.37%) that qualified for the Medicare program by age than AI/AN patients (77.15%). More NHW patients (83.78%) resided in urban areas than AI/AN (72.52%). And, most of the population resided in urban areas at cancer diagnosis than in rural areas.

Travel time to a chemotherapy, radiation, and surgical facility was greater for AI/AN colon cancer patients. More AI/AN (31.13%) had 60 minutes or more to access a chemotherapy facility than NHW (18.49%). In comparison to NHW patients (7.79%), AI/AN colon patients (13.25%) had to travel 60 minutes or more to a radiation facility. Larger percentage of AI/AN (10.26%) also had 60 minutes or more to travel to a surgical center than NHW (03.11%). AI/AN colon cancer patients (00.66%) had slightly increased travel time to a screening facility than NHW (00.16%).

Table 4.1: Bivariate Analyses of the Characteristics of AI/AN and NHW Colon Cancer Patients.

Variable	AI/AN N= 302 No. (%)	NHW N= 94,146 No. (%)	P-Value
Age at Diagnosis			
<=65	94 (31.13)	17,985 (19.10)	<0.0001
>65	208 (68.87)	76,161 (80.90)	
Mean Age at Diagnosis[1] (Range)	69.88 (28-98)	74.44 (22-106)	<0.0001
Sex			
Male	134 (44.37)	42,955 (45.63)	0.6620
Female	168 (55.63)	51,191 (54.37)	
Marital Status			
Single/Separate/Divorced	65 (21.52)	13,762 (14.62)	<0.0001
Married	133 (44.04)	49,233 (52.29)	
Widowed	80 (26.49)	27,376 (29.08)	
Unknown	24 (07.95)	3,775 (04.01)	
Income			
Median Income[2] (Range)	35,428 (12,507-115,434)	47,288 (7-200,008)	<0.0001
Reason for Entitlement			
Age	233 (77.15)	84,130 (89.37)	<0.0001
Disability or End Stage Renal Disease	69 (22.85)	10,005 (10.63)	
Cancer Stage			
Early	107 (35.43)	38,420 (40.81)	0.0517
Late	185 (61.26)	51,291 (54.48)	
Unstaged	10 (03.31)	4,435 (04.71)	
Cause of Death			
Alive	139 (46.03)	43,979 (46.71)	0.0729
Colon Death	94 (31.13)	26,385 (28.03)	
Other Cancer Death	16 (05.30)	3,173 (03.37)	
Other Cause of Death	53 (17.55)	20,609 (21,89)	

[1] Mean age is the same as the median age.
[2] Wilcoxon Test, two-sided (z= -18.7972)

Table 4.1: continued

Variable	AI/AN N= 302 No. (%)	NHW N= 94,146 No. (%)	P-Value
Median Survival Years (Range)	2.16 (0-16.92)	2.66 (0-17.01)	0.0913
Mean Survival Years (Range)	3.67 (0-16.92)	3.95 (0-17.01)	0.2214
Charlson Comorbidity Index[3]			
0	235 (77.81)	76,521 (81.28)	0.1506
1	37 (12.25)	11,122 (11.81)	
2	20 (06.62)	3,892 (04.13)	
3+	10 (03.31)	2,611 (02.77)	
Geographic Residence at Diagnosis			
Urban	219 (72.52)	78,877 (83.78)	<0.0001
Rural	83 (27.48)	15,269 (16.22)	
Travel Time to Chemotherapy			
< 30 minutes	168 (55.63)	55,714 (59.18)	<0.0001
30-60 minutes	40 (13.25)	21,029 (22.34)	
60+ minutes	94 (31.13)	17,403 (18.49)	
Travel Time to Radiation			
< 30 minutes	234 (77.48)	77,316 (82.12)	0.0020
30-60 minutes	28 (09.27)	9,497 (10.09)	
60+ minutes	40 (13.25)	7,333 (07.79)	
Travel Time to Surgery			
< 30 minutes	251 (83.11)	86,647 (92.03)	<0.0001
30-60 minutes	20 (06.62)	4,568 (04.85)	
60+ minutes	31 (10.26)	2,931 (03.11)	
Travel Time to Screening			
< 30 minutes	291 (96.36)	93,238 (99.04)	<0.0001
30-60 minutes	9 (02.98)	756 (00.80)	
60+ minutes	2 (00.66)	152 (00.16)	

[3] Window of time is 1 year prior to diagnosis through the month of diagnosis.

Race and Colon Cancer Survival

Table 4.2 contains results for geographic measures that may impact colon cancer mortality. Model 1 included both NHW and AI/AN and this model controlled for stage, age, sex, income, marital status, race, and comorbidity index. Model 2 was developed for the AI/AN population and model 3 was for NHW and they both had the same controls as Model 1, except for race.

Examining whether there were differences among race, the NHW model (model 3) found that travel time to screening was significant for this model. Traveling 60 minutes or more, in comparison to <30 minutes, to a colonoscopy or sigmoidoscopy screening facility indicated increased risk for colon cancer mortality among the NHW (HR=1.56, CI 1.16-2.09), whereas for AI/AN, screening and risk for colon cancer mortality was not statistically significant. In regards to AI/AN, it appears there is increased risk for colon cancer mortality for AI/AN living 60 minutes or more from a chemotherapy center (HR= 2.57, CI 1.39-4.76) (Model 2). Results for travel to chemotherapy for the NHW population was not statistically significant.

Stage, Race, and Colon Cancer Mortality

Tables 4.3, 4.4, and 4.5 are stage-specific models and in combination with travel time to appropriate treatment and screening. For instance, those only at distant stages should only be obtaining radiation treatment. Therefore, models (Table 4.4) were created for only those with distant stages and travel times to a radiation and screening center.

Table 4.3 includes results for those at regional and distant stages and the impact travel times to chemotherapy and screening centers have on colon cancer mortality. Model 1 includes both the AI/AN and NHW, Model 2 is AI/AN, and model 3 is NHW. Results show NHW living 60 minutes or more, in comparison to those who are living 30 minutes or less, from a screening

Table 4.2: Multivariate Cox Proportional Hazards Regression of Risk Factors Impacting Colon Cancer Mortality among AI/AN and NHW.

		Model 1 AI/AN and NHW N=94,448 D=26,479		Model 2 AI/AN N=302 D=94		Model 3 NHW N=94,146 D=26,385	
Variable	Attribute	HR (95% CI) N=94,448	P-Value	HR (95% CI) N=94,146	P-value	HR (95% CI) N=302	P-value
Cancer Stage at Diagnosis	Early	Ref	Ref	Ref	Ref	Ref	Ref
	Late	1.59 (1.55-1.63)	<0.0001	1.43 (0.85-2.41)	0.1813	1.59 (1.55-1.63)	<0.0001
	Unstaged	2.41 (2.26-2.57)	<0.0001	3.44 (0.94-12.44)	0.0607	2.41 (2.26-2.57)	<0.0001
Age at Diagnosis		1.03 (1.03-1.03)	<0.0001	1.04 (1.01-1.07)	0.0029	1.03 (1.03-1.03)	<0.0001
Sex	Female	Ref	Ref	Ref	Ref	Ref	Ref
	Male	1.16 (1.12-1.19)	<0.0001	1.19 (0.71-2.00)	0.5182	1.16 (1.12-1.19)	<0.0001
CT Income		0.99 (0.98-0.99)	0.0002	0.87 (0.71-1.07)	0.1900	0.99 (0.98-0.99)	0.0002
Marital Status	Single[4]	1.20 (1.16-1.25)	<0.0001	1.62 (0.84-3.12)	0.1473	1.20 (1.16-1.25)	<0.0001
	Married	Ref	Ref	Ref	Ref	Ref	Ref
	Widowed	1.10 (1.06-1.14)	<0.0001	1.04 (0.54-2.02)	0.8976	1.10 (1.06-1.14)	<0.0001
	Unknown	1.01 (0.95-1.08)	0.7216	1.19 (0.52-2.73)	0.6876	1.01 (0.94-1.08)	0.7706
CCI	0	Ref	Ref	Ref	Ref	Ref	Ref
	1	1.36 (1.31-1.42)	<0.0001	1.25 (0.54-2.91)	0.6059	1.36 (1.31-1.42)	<0.0001
	2	1.69 (1.58-1.81)	<0.0001	1.11 (0.47-2.63)	0.8062	1.69 (1.58-1.81)	<0.0001
	3+	2.26 (2.09-2.45)	<0.0001	3.32 (0.96-11.48)	0.0581	2.26 (2.08-2.44)	<0.0001

[4] Single, separated or divorced.
[a] For Model 2, the sample size was 2 for the >=60 min category. The individual was included in the <60 min category.

Table 4.2: continued

		Model 1 AI/AN and NHW N=94,448 D=26,479		Model 2 AI/AN N=302 D=94		Model 3 NHW N=94,146 D=26,385	
Variable	Attribute	HR (95% CI) N=94,448	P-Value	HR (95% CI) N=94,146	P-value	HR (95% CI) N=302	P-value
Race	NHW	Ref	Ref				
	AI/AN	1.14 (0.90-1.43)	0.2773				
Geographic Residence	Urban	Ref	Ref	Ref	Ref	Ref	Ref
	Rural	0.99 (0.96-1.03)	0.7550	0.80 (0.45-1.44)	0.4633	1.00 (0.96-1.03)	0.7759
Travel Time to Chemotherapy	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
	<60 Min	1.00 (0.97-1.03)	0.8874	0.66 (0.27-1.59)	0.3506	1.00 (0.97-1.03)	0.9021
	60+ Min	1.02 (0.98-1.06)	0.3630	2.57 (1.39-4.76)	0.0028	1.02 (0.98-1.06)	0.4519
Travel Time to Radiation	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
	<60 Min	0.98 (0.94-1.04)	0.5321	1.27 (0.44-3.70)	0.6721	0.98 (0.94-1.03)	0.5229
	60+ Min	0.98 (0.92-1.05)	0.5599	0.40 (0.09-1.86)	0.2376	0.98 (0.92-1.05)	0.5804
Travel Time to Surgery	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
	<60 Min	0.99 (0.92-1.06)	0.7770	0.58 (0.16-2.09)	0.4023	0.99 (0.92-1.06)	0.7985
	60+ Min	0.92 (0.83-1.01)	0.0863	1.38 (0.30-6.30)	0.6756	0.92 (0.83-1.01)	0.0733
Travel Time to Screening	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
	<60 Min	0.98 (0.84-1.13)	0.7668	1.41 (0.49-4.03)	0.5238	0.97 (0.83-1.12)	0.6650
	60+ Min	1.55 (1.15-2.08)	0.0036			1.56 (1.16-2.09)	0.0031

Table 4.3: Multivariate Cox Proportional Hazards Regression of the Impact of Travel Time to Chemotherapy, Surgery, and Screening on Colon Cancer Mortality by Regional and Distant Stages.

		Model 1 AI/AN & NHW N= 51,476 D= 21,233		Model 2 AI/AN N= 185 D= 76		Model 2 NHW N= 51,291 D= 21,157	
		HR (95% CI)	p-value	HR (95% CI)	p-value		p-value
Stage	In situ	--	--	--	--	--	--
	Localized	--	--	--	--	--	--
	Regional	Ref	Ref	Ref	Ref	Ref	Ref
	Distant	3.33 (3.21-3.47)	<0.0001	7.25 (3.08-17.07)	<0.0001	3.33 (3.20-3.46)	<0.0001
	Unstaged	--	--	--	--	--	--
Age at Dx		1.03 (1.03-1.04)	<0.0001	1.05 (1.01-1.08)	0.0110	1.03 (1.03-1.04)	<0.0001
Sex	Female	Ref	Ref	Ref	Ref	Ref	Ref
	Male	1.14 (1.10-1.18)	<0.0001	1.15 (0.56-2.35)	0.6970	1.14 (1.10-1.18)	<0.0001
CT Income		0.98 (0.97-0.99)	0.0002	0.80 (0.62-1.04)	0.0972	0.98 (0.97-0.99)	0.0003
Marital Status	Single[5]	1.20 (1.14-1.26)	<0.0001	1.25 (0.45-3.46)	0.6705	1.20 (1.14-1.26)	<0.0001
	Married	Ref	Ref	Ref	Ref	Ref	Ref
	Widowed	1.06 (1.02-1.11)	0.0084	1.83 (0.78-4.31)	0.1686	1.06 (1.02-1.11)	0.0096
	Unknown	1.18 (1.07-1.30)	0.0009	1.79 (0.59-5.47)	0.3066	1.18 (1.07-1.30)	0.0012
[a]CCI[6]	0	Ref	Ref	Ref	Ref	Ref	Ref
	1	1.31 (1.23-1.38)	<0.0001	2.05 (0.70-5.97)	0.1884	1.31 (1.23-1.38)	<0.0001
	2	1.63 (1.49-1.79)	<0.0001	0.61 (0.14-2.68)	0.5090	1.64 (1.49-1.80)	<0.0001
	3+	1.96 (1.74-2.21)	<0.0001			1.97 (1.74-2.14)	<0.0001

[5] Single, separated or divorced.
[6] Window of time is 1 year prior to diagnosis through the month of diagnosis.
[a] For model 2, the sample size was 5 for the 3+ category. These 5 people were included in the 2 category.
[B] For model 2, the sample size was 1 for the >=60 min category. The individual was included in the <60 min category.

Table 4.3: continued

		Model 1 AI/AN & NHW N= 51,476 D= 21,233		Model 2 AI/AN N= 185 D= 76		Model 2 NHW N= 51,291 D= 21,157	
		HR (95% CI)	p-value	HR (95% CI)	p-value		p-value
Race	NHW	Ref	Ref				
	AI/AN	1.06 (0.79-1.43)	0.6937				
Geographic Residence	Urban	Ref	Ref	Ref	Ref	Ref	Ref
	Rural	1.03 (0.98-1.08)	0.2340	1.12 (0.53-2.34)	0.7731	1.03 (0.98-1.08)	0.2366
Travel Time to Chemotherapy	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
	30-60 Min	0.98 (0.94-1.02)	0.3618	0.36 (0.08-1.62)	0.1812	0.98 (0.94-1.03)	0.3765
	60+ Min	1.01 (0.96-1.06)	0.7653	2.43 (1.03-5.77)	0.0436	1.01 (0.96-1.06)	0.8221
Travel Time to Surgery	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
	30-60 Min	0.96 (0.88-1.04)	0.3181	0.61 (0.14-2.68)	0.5168	0.96 (0.88-1.05)	0.3563
	60+ Min	0.92 (0.83-1.02)	0.1246	0.52 (0.16-1.66)	0.2682	0.92 (0.82-1.02)	0.1105
[b]Travel Time to Screening	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
	30-60 Min	0.87 (0.71-1.07)	0.1957	1.86 (0.51-6.81)	0.3511	0.86 (0.69-1.06)	0.1474
	60+ Min	1.60 (1.09-2.34)	0.0171			1.60 (1.09-2.35)	0.0162

Table 4.4: Multivariate Cox Proportional Hazards Regression of the Impact of Travel Time to Surgery and Screening on Colon Cancer Mortality by Distant Stage.

Variable	Attribute	Model 1 AI/NHW N= 17,799 D= 1,456 HR (95% CI)	p-value	Model 2 AI/AN N= 74 D= 2 HR (95% CI)	p-value	Model 3 NHW N=17,725 D= 1,454 HR (95% CI)	p-value
Age at Dx		1.03 (1.03-1.04)	<0.0001	1.17 (1.06-1.30)	0.0017	1.03 (1.03-1.04)	<0.0001
Sex	Female	Ref	Ref	Ref	Ref	Ref	Ref
	Male	1.08 (1.01-1.15)	0.0233	1.41 (0.31-6.50)	0.6563	1.08 (1.01-1.15)	0.0213
CT Income		0.97 (0.95-0.99)	0.0001	0.76 (0.45-1.27)	0.2903	0.97 (0.95-0.99)	0.0001
Marital Status	Single[7]	1.18 (1.09-1.29)	<0.0001	0.51 (0.11-2.47)	0.4005	1.19 (1.09-1.29)	<0.0001
	Married	Ref	Ref	Ref	Ref	Ref	Ref
	Widowed	1.07 (0.99-1.15)	0.1081	0.76 (0.10-5.74)	0.7935	1.07 (0.99-1.15)	0.0918
	Unknown	1.28 (1.08-1.50)	0.0035	0.41 (0.02-9.17)	0.5759	1.27 (1.08-1.50)	0.0039
[a]CCI[8]	0	Ref	Ref	Ref	Ref	Ref	Ref
	1	1.21 (1.10-1.32)	<0.0001	10.27 (1.45-72.88)	0.0198	1.20 (1.10-1.32)	<0.0001
	2	1.48 (1.27-1.72)	<0.0001	3.97 (0.27-58.23)	0.3147	1.48 (1.27-1.72)	<0.0001
	3+	1.50 (1.23-1.83)	<0.0001			1.51 (1.24-1.84)	<0.0001
Race	NHW	Ref	Ref				
	AI/AN	1.18 (0.73-1.90)	0.5059				
Geographic Residence	Urban	Ref	Ref	Ref	Ref	Ref	Ref
	Rural	1.04 (0.96-1.13)	0.3455	2.21 (0.48-10.25)	0.3114	1.04 (0.96-1.13)	0.3732

[7] Single, separated or divorced.
[8] Window of time is 1 year prior to diagnosis through the month of diagnosis.
[a] For model 2, the sample size was 3 for the 3+ category. These 3 people were included in the 2 category.
[B] For model 2,, the sample size was 2 for the <60 min category and 0 for the >=60 min category. The potential screening variable was dropped for Model 2.

Table 4.4: continued

Variable	Attribute	Model 1 AI/NHW N= 17,799 D= 1,456 HR (95% CI)	p-value	Model 2 AI/AN N= 74 D= 2 HR (95% CI)	p-value	Model 3 NHW N=17,725 D= 1,454 HR (95% CI)	p-value
Travel Time to Radiation	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
	30-60 Min	0.95 (0.86-1.05)	0.3129	0.81 (0.09-7.71)	0.8553	0.95 (0.86-1.05)	0.3260
	60+ Min	1.06 (0.95-1.18)	0.3281	5.74 (0.65-50.92)	0.1167	1.06 (0.95-1.18)	0.3298
[a]Travel Time to Screening	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
	30-60 Min	0.92 (0.66-1.28)	0.6345	0.87 (0.04-19.96)	0.9317	0.92 (0.65-1.29)	0.6143
	60+ Min	1.42 (0.76-2.67)	0.2703			1.42 (0.76-2.66)	0.2720

Table 4.5: Multivariate Cox Proportional Hazards Regression of the Impact of Surgery and Screening Travel Times on Colon Cancer Mortality by All Stages.

		Model 1 AI/AN & NHW N= 94,448 D= 26,479		Model 2 AI/AN N= 302 D= 94		Model 3 NHW N=94,146 D= 26,385	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Stage	In situ	Ref	Ref	Ref	Ref	Ref	Ref
	Localized	1.11 (1.04-1.18)	0.0020	1.80 (0.59-5.55)	0.3055	1.10 (1.04-1.18)	0.0023
	Regional	1.33 (1.24-1.41)	<0.0001	1.64 (0.52-5.11)	0.3964	1.32 (1.24-1.41)	<0.0001
	Distant	4.64 (4.33-4.96)	<0.0001	7.49 (2.16-26.96)	0.0015	4.63 (4.33-4.96)	<0.0001
	Unstaged	2.76 (2.54-3.00)	<0.0001	5.25 (1.04-26.63)	0.0452	2.76 (2.53-3.00)	<0.0001
Age at Dx		1.04 (1.03-1.04)	<0.0001	1.05 (1.02-1.08)	0.0002	1.04 (1.03-1.04)	<0.0001
Sex	Female	Ref	Ref	Ref	Ref	Ref	Ref
	Male	1.14 (1.11-1.17)	<0.0001	1.23 (0.73-2.09)	0.4381	1.14 (1.11-1.17)	<0.0001
CT Income		0.99 (0.98-0.99)	<0.0001	0.86 (0.70-1.06)	0.1513	0.99 (0.98-0.99)	<0.0001
Marital Status	Single[9]	1.19 (1.15-1.24)	<0.0001	1.39 (0.71-2.72)	0.3325	1.19 (1.15-1.24)	<0.0001
	Married	Ref	Ref	Ref	Ref	Ref	Ref
	Widowed	1.09 (1.05-1.13)	<0.0001	0.94 (0.48-1.86)	0.8586	1.09 (1.05-1.13)	<0.0001
	Unknown	1.02 (0.95-1.09)	0.5741	1.04 (0.44-2.49)	0.9246	1.02 (0.95-1.09)	0.6041
CCI[10]	0	Ref	Ref	Ref	Ref	Ref	Ref
	1	1.37 (1.32-1.43)	<0.0001	0.99 (0.43-2.27)	0.9728	1.37 (1.32-1.43)	<0.0001
	2	1.74 (1.63-1.86)	<0.0001	1.34 (0.57-3.16)	0.5003	1.75 (1.63-1.87)	<0.0001
	3+	2.35 (2.17-2.55)	<0.0001	3.29 (0.94-11.56)	0.0638	2.35 (2.17-2.55)	<0.0001

[9] Single, separated or divorced.
[10] Window of time is 1 year prior to diagnosis through the month of diagnosis.
[a] For model 2,, the sample size was 2 for the >=60 min category. The 2 people were added into the <60 min category.

Table 4.5: continued

		Model 1 AI/AN & NHW N= 94,448 D= 26,479		Model 2 AI/AN N= 302 D= 94		Model 3 NHW N=94,146 D= 26,385	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Race	NHW	Ref	Ref				
	AI/AN	1.15 (0.92-1.45)	0.2318				
Geographic	Urban	Ref	Ref	Ref	Ref	Ref	Ref
Residence	Rural	0.99 (0.96-1.03)	0.6007	0.84 (0.47-1.51)	0.5625	0.99 (0.96-1.03)	0.6160
Travel Time	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
to Surgery	30-60 Min	0.99 (0.93-1.05)	0.6559	0.73 (0.28-1.92)	0.5166	0.99 (0.93-1.05)	0.6826
	60+ Min	0.93 (0.86-0.997)	0.0409	1.40 (0.67-2.95)	0.3733	0.92 (0.85-0.99)	0.0307
[a]Travel Time	<30 Min	Ref	Ref	Ref	Ref	Ref	Ref
to Screening	30-60 Min	0.94 (0.81-1.09)	0.4345	1.24 (0.41-3.78)	0.6999	0.94 (0.81-1.09)	0.3879
	60+ Min	1.58 (1.17-2.12)	0.0025			1.59 (1.18-2.13)	0.0022

center increases one's risk for a colon cancer death for those at regional or distance stages (HR= 1.60, CI 1.09-2.35). As for AI/AN, the results were not significant for travel time to chemotherapy. More importantly for the AI/AN, travel time to chemotherapy was more of an impact. In comparison to living 30 minutes or less, AI/AN living 60 minutes or more to a chemotherapy center had an increased risk for colon cancer mortality (HR=2.43, CI 1.03-5.77).

Table 4.4 displays results of those at distant stage and travel times to a radiation and a screening center and their risk for colon cancer mortality. For all the models, none of the geographic measures were significant.

Results for risk for colon cancer mortality among those at all stages and travel times to surgery and screening centers can be found in Table 4.5. Results in model 3 demonstrate less risk for colon cancer mortality among NHW living 60 minutes or more to a surgical center than those living less than 30 minutes (model 3) (HR= 0.92, CI 0.85-0.99). There is also increased risk for colon cancer mortality among NHW at all stages and living 60 minutes or more from a screening facility than those living less than 50 minutes (HR= 1.59, CI 1.18-2.13). The results for the AI/AN population (model 2) demonstrated nonsignificant results.

Discussion

In terms of risk for colon cancer mortality, the effects of travel time to treatment and screening have not been fully investigated, especially among AI/AN. Furthermore, risk factor knowledge for colon cancer mortality among the AI/AN population is sparse because of limited studies.

Rural/Urban, Travel Time, and Access

Many cancer studies often use rural/urban residence as a variable to examine geographic access. However, in all the combined race models (Models 1 in Tables 4.2, 4.3, 4.4, and 4.5), after controlling for various risk factors, geographic residence was not significant and for the models, the relative risk for rural, in comparison to urban, hovered around 1.00. Models were also built excluding travel times and rural status, in comparison to urban status, was not significant and relative risks also hovered around 1.00 (results were not presented.) In this study, both rural and urban residents had travel times in all three travel time strata: <30, 30-60 and 60+ minutes. It appears that using travel times is a more accurate measure than using rural/urban measures. Furthermore, using travel times to treatment and screening gives a more accurate picture to which type of service may be most important for a population, rather than using rural/urban measures.

Race and Colon Cancer Mortality

AI/AN who live 60 minutes or more to the nearest chemotherapy center have an elevated risk for colon cancer mortality (Table 4.2). Therefore, it appears there is a difference in colon cancer survival between AI/AN and NHW who have to travel 60 minutes or more for chemotherapy services. AI/AN may have a more difficult time accessing chemotherapy treatment and/or following through on treatment compliance, which may be due to lack of transportation and/or road conditions. AI/AN living on reservations may also have a more difficult time traveling during winter months, especially if they live a distance from an asphalt road.

Models 1 in Tables 4.2-4.4 include race (AI/AN and NHW) as a risk factor for colon cancer mortality. Each of these models suggests AI/AN have an increase risk for colon cancer

mortality after controlling for a number of factors, in comparison to NHW. However, in each model, the results were not statistically significant, which may be due to a small sample size for AI/AN. The issue of race as a risk factor needs to be explored further. Other studies have found disparities in cancer treatment among races and these differences were to treatment, biology, and knowledge/beliefs.[13,31-41] The issue of small sample size will always be an issue since the AI/AN population will always be smaller than NHW, so exploration of race might continue to be a problem.

Stage and Colon Cancer Mortality

The models that examine the impact of travel times to treatment and screening by various stages can be found in Tables 4.3-4.5. When examining the models, there are not only differences by race but also stage at diagnosis.

For AI/AN at regional and distant stages, having to travel 60 minutes or more to obtain chemotherapy negatively impacts their survival (Table 4.3, Model 2), whereas for NHW, travel time to chemotherapy did not impact their survival. These results need to be explored more thoroughly to understand the mechanism(s) that are influencing poor survival among the AI/AN population who are at regional and distant stages and having to travel 60 minutes or more to obtain chemotherapy.

For NHW at all stages, distance to screening and surgery had the largest impact on survival for them (Table 4, Model 3). Therefore, the data suggest that 6o minutes or more of driving time to screening negatively impacts colon cancer mortality. A diagnostic or treatment colonoscopy is an involved process and if you have a long travel time, the preparation and procedure may potentially be a barrier for a colonoscopy.

Results also indicate that those living 60 minutes or more from a surgical center are 7% less likely at risk for a colon cancer death. Decreased risk may be due to surgical practices or differences in patients in rural areas. It has been found that rural surgeons performed more endoscopic procedures than urban surgeons and this surgical experience may decrease complications and/or death.[42] An additional study found that complications and reoperation rates were higher in urban centers than rural centers and that urban centers had sicker patients.[43] Higher complications, reoperation rates, and sicker patients may contribute to higher death in urban areas. Surgical procedures might also be different for rural or for patients living a distance from a surgical center. For instance, in a breast cancer study, it was found that those living further away underwent more mastectomies than breast conserving surgery, along with radiotherapy.[44]

Limitations

The population is a Medicare population and they have different characteristics than the general population. This study population potentially has more urban elderly and they live in more affluent areas, suggesting a higher income population.[45] Since this population is a Medicare population, they have Medicare coverage, whereas many in cancer patients do not have coverage.

There may be underestimation of treatment distances for the AI/AN population. Reservations do not have street addresses and many AI/AN obtain mail from their nearest post office. For this study, patient's census tracts are determined from zip codes and post offices are located in areas that have a larger concentration of people. Most likely, some of the areas that have post offices also have a health provider that may (or may not) provide treatment and screening procedures.

The screening travel times are also most likely underestimated. The centroids were determined using the addresses of treatment providers within the zip code areas of providers offering screening procedures. This method would overestimate screening providers and thus would increase screening facilities for all. This might be more problematic in less populated areas since the census tracts and zip code areas are larger in less populated areas.

Conclusion

Travel time rather than rural/urban status gives a better picture to determine risk for colon cancer mortality. Living 60 minutes or more to obtain screening is risk for colon cancer mortality across various stages for the NHW population. Access to screening may need to be targeted for those who have to travel longer distances rather than targeting whether a person lives in a rural or urban area. Further travel time to a surgical center appears to show a slightly lower risk for colon cancer mortality. However, this lower risk needs to be explored further to determine if there are differences in those further for surgical procedures. Chemotherapy access needs to be further explored and addressed for AI/AN having to travel further distances. Chemotherapy is not a one-time treatment and it may be extremely difficult for those living further to access this service. Having transportation options may be a way to create greater chemotherapy access.

Appendix A

Table 4.6: Medicare claims codes for surgery, radiation and chemotherapy.

Author	Years	Surgery	Radiation	Chemotherapy
Baldwin, et al.[46]	Patients: 1992-1996 Claims: 1992-1997			J0640, J9190, 96408-96414, 96520, 96530, 96545, 96549, Q0083-Q0085, E0781, E933.1, V58.1, V66.2, V67.2, 99.25
Baldwin, et al.[47]	Patients: 1992-1996 Claims: 1991-1997		77261-77499, 77750-77799, V58.0, V66.1, V67.1, 92.20-92.29, 0330, 0333, 0339	
Bradley, et al.[48]	Patients: 1997-2000 Claims: 1997-2001			96400-96599, Q0083-Q0085, J0640, J8510, J8520, J8521, J8530-J8999, J9000-J9999, E0781, E9331, V58.1
Cen, et al.[49]	Patients: 2003-2005 Claims: 2003-2006			96400–96549, J8510, J8520, J8521, J8530–J8999, J9000–J9999, Q0083–Q0085, 9925, V58.1, V66.2, V67.2, 0331, 0332, 0335

Table 4.6: continued

Author	Years	Surgery	Radiation	Chemotherapy
Cheung, et al.[50]	Patients: 1991-2002 Claims: 1991-2003		77xxx, 79xxx, S8049, V58.0, 92.2X, 0330, 0333, 0339	964XX, 9651X-9654X, C1166, C1167, C1178, C9110, C9205, C9207, C9213-C9216, C9411, C9414-C9419, C942x, C9430-C9438, G0355, G0356, G0359-G0362, J7150, J85xx-J87xx, J9xxx, J8999, Q0083, Q0085, S9325-S9329, S933x-S937x, S9494-S9497, V58.1, 99.25, 0331, 0332, 0335
HCPCS Website: 2010 Codes[51]				J8999, J9000-J9999, J8500-J9999, Q0083-Q0085
Cummings, et al.[52]	Patients: 1996-2005 Claims: 1996-2009		77xxx, 92.2, V58.0, V66.1, V67.1	964xx, 965xx, G0355-G0363, J9000-J9999, Q0083-Q0085, 99.25, V58.1, V67.2, V66.2, 0331, 0332, 0335
Davidoff, et al.[53]	Patients: 1997-2002 Claims: 1996-2002			C9205, J8520, J8521, J9190, J9206, J9263
Dobie, et al.[54]	Patients: 1992-1996 Claims: 1991-1998			96408, 96410, 96412, 96414, 96520, 96530, 96545, 96549, J0640, J9190, Q0083-Q0085, 99.25, E0781, V58.1

Table 4.6: continued

Author	Years	Surgery	Radiation	Chemotherapy
Dobie, et al.[55]	Patients: 1992-1999 Claims: 1992-2004		77331-77334, 77336, 77370, 77399, 77402-77417, 77419-77431, 77499, 92.20, 92.23-92.36, 92.29, V58.0, 0333	96408, 96410, 96412, 96414, 96545, 96549, 96520, 96530, J0640, J9190, Q0083-Q0085, 99.25, E0781, V58.1
Du, et al.[56]	Patients: 1992 Claims: 1991		77401–77499 or 77750–77799, 9221-9229, 0330, 0333	
Du, et al.[57]	Patients: 1991-1992 Claims:			9925, 96400- 96549, 0331, J9000-J9999, Q0083-Q0085, V58.1, V66.2, V67.2
Du, et al.[58]	Patients: 1992-1999 Claims:	44140–44160, 45383–45385, 45.71–45.76, 5.79-45.89, 48.41, 48.49–48.69		
Etzioni, et al.[59]	Patients: 1992-2002 Claims: ~1991-2002	44140–44145-44147, 4150–44160, 44204-44212, 44300, 44310, 44320, 44322, 44340, 44345, 44346, 44312, 44314, 44316, 44605, 44620-44626, 45005, 45020, 45100, 45108, 45110–45135, 45395-45397, 45562, 46020, 46030, 6040-46060, 46080, 46083, 46200, 46210, 46211, 46220, 46221, 46230, 46250-46262, 6270-46288, 46320, 46500, 46700, 46706, 46750-46762, 6900-46924, 46934-46936, 46940, 46942, 46945, 46947		

Table 4.6: continued

Author	Years	Surgery	Radiation	Chemotherapy
Fitzgerald, et al.[60]	Patients: 1997-2000 Claims: 1996-2000	44139, 44158-44160, 44140-44147, 44150-44160, 44394		
Galandiuk, et al.[61]	Patients: Claims: 1998-2003	44140, 44141, 44143- 44146, 44153, 44155, 44156, 44160, 45110, 45111, 45113, 45116, 45119, 45130		
Gross, et al.[62]	Patients: 1992-2002	44140-44147	77400-77499, 77750-77799, V58.0, V66.1, V67.1, 92.20–92.26, 92.29	44140-44147, 45.71, 45.73-45.95, 48.41-48.69
Howard, et al.[63]	Patients: 1995-2005 Claims: 1995-2006			964XX, 965XX, Q0083-Q0085, G0355, G0359, V58.1, V66.2, V67.2, 99.25
Keating, et al.[64]	Patients: 2001-2004 Claims:	44110, 44111, 44140-44160, 44392, 44393, 44394, 5110-45121, 45126, 45160-45170, 45190, 45308, 45309, 45315, 45320, 45333, 45338, 45339, 45383-45385, 45.41-45.42, 45.60, 45.71-45.76, 45.79-45.89, 46.04, 48.35, 48.36, 48.40, 48.41, 48.49-48.69	77261-77431, 77499, 77750-77797, 92.2-92.29 V58.0, V67.1, V66.1, 0330, 0333	30070, 50145, 50146, J9190, J8520, J8521, 99.25
Lang, et al.[65]	Patients: 1991-2000 Claims: 1991-2005		77401-77499, 77750-77799, V58.0, V66.1, V67.1, 92.21-92.29	51720, 964xx, 965xx, J7150, J8510, J8520, J8521, J8530-J8999, J9000-J9999, Q0083-Q0085, V58.1, V66.2, V67.2, 99.25

Table 4.6: continued

Author	Years	Surgery	Radiation	Chemotherapy
Lund, et al.[66]	Patients: 2000 & 2005 Claims: 2000, 2002, 2005			J8520, J8521, J9035, J9055, J9190, J9206, J9263, C9205, C9214, C9215, C9257, Q2024, S0116, V58.1, V66.2, V67.2, 99.25
Meyerhardt, et al.[67]	Patients: 2002-2007 Claims: 2002-2009			J8520, J8521, J9035, J9055, J9190, J9206, J9263, J9303, J9999, C9215, C9235
Obeidat, et al.[68]	Patients: 1998-2002 Claims:	32440, 32442, 32445, 32480, 32482, 32484, 32500, 32520, 44139-44160, 44204-44213, 45110-45126, 47120-47130, 47300, 47380-47382, 51597, 58240, 45.70, 45.80, 48.40-48.60	77401-77799, 92.21-92.29, V58.0, V66.1, V67.1, 0330, 0333, 0339	964xx, 965xx, 51720, 0331, 0332, 0335, 99.25, J0640, J8510, J8520, J8521, J8530-J8999, J9190, J9200, J9206, Q0083-Q0085, V58.1, V66.2, V67.2
O'Connor, et al.[69]	Patients: 1992-2005 Claims: 1991-2005		77401-77499, 77750-77799, V58.0, V66.1, V67.1, 92.21-92.29, 0330, 0333	C8953-8955, E0781, E9331, G0355-G0363, J0640, J8510, J8520, J8521J8530-J8999, J9000-J9999, J9190, J9200, J9206, J9263, Q0177, Q0083-Q0085, S9329-9331, V58.1, V66.2, V67.2, 99.25. 0331, 0332, 0335

Table 4.6: continued

Author	Years	Surgery	Radiation	Chemotherapy
Paulson, et al.[70]	Patients: 1996-2003	44140, 44141, 44143-44147, 44150, 44152, 44155, 44160, 44204-44208, 44210, 44212, 45110-45114, 45116, 45119, 45123, 45126, 45160, 45170, 45395, 45397, 45.70, 45.71, 45.72, 45.73, 45.74, 45.75, 45.76, 45.79, 45.80, 48.35, 48.40, 48.41, 48.49, 48.50, 48.60, 48.61, 48.62, 48.63, 48.64, 48.65, 48.69		
Wright, et al.[71]	Patients: 1995-2005 Claims:			Q0136, Q0137, J0880-J0882, J0885, J0886
SEER-Medicare Website			77401-77499, 77520, 77523, 77750-77799, G0256, G0261, V58.0, V66.1, V67.1, 92.21-92.29, 0330, 0333	51720, 964xx, 96400-96549, Q0083-Q0085, V58.0, V66.2, V67.1, 92.21-92.29, 0330, 0333

Appendix B

Table 4.7: Medicare claims codes for colonoscopy and sigmoidscopy.

Author	Years	Colonoscopy Screening	Sigmoidoscopy Screening
Benarroch-Gampel, et al.[72]	Sample: 2007 Claims: 2002-2007	44388, 33489, 44392, 44393, 44394, 45394, 45378, 45380, 45382, 45383, 45384, 45385 G0105, G0121, 45.23, 45.25, 45.27, 45.41, 45.42, 45.43, 48.36	
Cooper & Kou.[73]	Sample: 1998 Claims: 1993-1998	44388, 44389, 44392, 44393, 44394, 45378, 45380, 45382, 45383, 45384, 45385, G0105, G0121, 45.23, 45.25, 45.41, 45.42, 45.43, 48.36	45330, 45331, 45333, 45338, 45339, G0104
Fenton, et al.[74]	Sample: 1995-2003. Claims:	45378, 45380, 45382, 45383, 45384, 45385, G0105, G0121, 45.21-45.23, 45.25	45300, 45305, 45308, 45309, 45315, 45317, 45320, 45330, 45331, 45333, 45334, 45338, 45339, G0104, 45.24, 48.23, 48.24
HHS Guide[75]	Claims: 1/2005-12/31/2006	G0105, G0121	G0104
HHS Guide[76]	1/2007-12/31/2008	G0105, G0121	G0104
HHS Guide[77]	1/2009-12/31/2010	G0105, G0121	G0104
Khiani, et al.[78]	Sample: 2001-2005	44388, 44389, 44392, 44393, 44394, 45378, 45379, 45380, 45382, 45383, 45384, 45385, 45.23, 45.25, 45.41-3, 48.36	45300-45327, 45330-45342, 45345, G0104, 45.24, 48.21-4
Schenck, et al.[79]	Sample: 1998-2005 Claims: 1998-2005	44388-44394, 44397, 45355, 45378-45387, G0105, G0121	45300, 45303, 45305, 45307, 45308, 45309, 45327, 45330, 45331, 45332, 45333, 45334, 45337, 45338, 45339, 45340, 45341, 45342, 45345, G0104, 45.24, 45.42, 48.21-48.25
Semrad, et al.[80]	Sample: 2003 Claims: 1998-2005	45378, 45380, 45382, 45383, 45384, 45385, G0105, G0121, 45.23, 45.25, 45.42, 45.43, 48.36	45300, 45305, 45308, 45309, 45315, 45317, 45320, 45330, 45331, 45333, 45334, 45338, 45339, G0107, 45.24, 48.23, 48.24

Table 4.7: continued

Author	Years	Colonoscopy Screening	Sigmoidoscopy Screening
Sima, et al.[81]	Sample: 1998-2005 Claims: 1998-2007	G0105, G0121	G0104

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CHAPTER 5

CONCLUSION

The overall purpose of the study was to determine colon cancer risk factors among American Indians/Alaska Natives (AI/AN) and Whites/Non-Hispanic Whites (NHW). Risk factors for colon cancer mortality were determined by utilizing current literature and through the development of a study that specifically examined the impact of race, comorbidities, travel time to screening, and travel time to treatment.

Race

The systematic review revealed that race was the only risk factor explored among American Indians/Alaska Natives (AI/AN) and the majority of the results were not significant, but all suggested an increased risk for colorectal or all-cause mortality among AI/AN. Risk ranged from HR = 1.10-1.50 (Table 2.4), whereas in the White population, numerous risk factors impacting colon cancer mortality have been investigated more thoroughly.

Race was examined in Chapters 3 and 4 and the hypothesis was to show an increased risk for colon cancer mortality among AI/AN. The results indicated increased risk for AI/AN, after controlling for various covariates, but results were nonsignificant. The range of risk for colon cancer mortality among AI/AN ranged from HR=1.06-1.18 (Tables 3.2, 4.2-4.5). Results being nonsignificant most likely is due to the smaller

sample size of AI/AN, in comparison to the NHW population. The increased colon cancer risk for AI/AN suggests that there may be other factors impacting race differentially and this needs to be further explored among AI/AN. However, sample size will always be an issue with the AI/AN population and it will continue to be an issue to detect effects of race.

Cormorbidity

Studies have examined the impact of comorbidity on colon cancer, colorectal cancer, or all-cause mortality.[1-4] Various comorbidity measures were used in these studies and their findings support the findings in this dissertation. An increase in comorbidity measure has a negative impact on colon cancer survival. Although not every study had statistically significant results, the risk for colon cancer, colorectal cancer, or all-cause mortality increased as comorbidity measure increased.

The hypothesis was to demonstrate an increase risk for colon cancer mortality among those with comorbidities. The results found NHW whose comorbidity index increased had an increased risk for colon cancer mortality (Table 3.2, Model 3). The NHW results were statistically significant. Results for the AI/AN were not statistically significant. Nonsignificance for AI/AN was most likely due to small sample size.

Travel Time to Treatment and Screening

The examination of travel times to treatment (colonoscopy, radiation, and surgery) and travel time to screening (colonscopy and sigmoidoscopy) and their impact on colon cancer mortality were also examined. The hypothesis of the study was for increased risk for colon cancer mortality for those traveling longer distances to treatment

and screening. The NHW model (Table 4.2, Model 3) demonstrated that those traveling 60 miles or more, rather than those traveling less than 30 minutes, to a screening facility had increased risk for colon cancer mortality. For AI/AN traveling 60 minutes or more, rather than those traveling less than 30 minutes, to a chemotherapy center had an increased risk for colon cancer mortality (Table 4.2, Model 2).

The examination of treatment and screening by various stages had different results. NHW traveling more than 60 minutes to screening and who were at regional or distant stage had higher risk for colon cancer mortality than NHW at regional or distant stage and traveling less than 30 minutes. Results for AI/AN at regional and distant stages were different than the NHW regional and distant stages (Table 4.3). AI/AN traveling more than 60 minutes to chemotherapy had an increased risk for colon cancer mortality, than AI/AN traveling less than 30 minutes.

The all stages models indicated that distance to screening was the most important factor for NHW. An additional result, which had contradictory findings, was distance to surgery. NHW at all stages who had to travel 60 minutes or more to screening had an increased risk for colon cancer mortality than NHW who traveled less than 30 minutes (Table 4.5, Model 3). NHW at all cancer stages who had to travel 60 minutes or more to surgery had lower risk for colon cancer mortality than who traveled less than 30 minutes.

These results represent the importance of examining data by race and stage along with race. There is definitely a differential in access for AI/AN and NHW and by cancer stage. The results for the AI/AN population suggest that access to chemotherapy for those living 60 miles or further needs to be explored further. What makes this population unique that it impedes chemotherapy uptake or compliance? Furthermore, for NHW the

issue appears to be access to screening. Those living further away appear to have problems with uptake of screening. This most likely is also an issue for the AI/AI population and it would benefit our communities if outreach activities targeted those living further away. And NHW living further from a surgical center having less risk need further exploration. Are there benefits to living further away?

Summary

There have been few studies that have examined travel time to treatment (radiation and surgery) and to the author's knowledge, no studies examining travel time to screening. Travel time to CRC treatment and its impact on survival has mainly been explored in other countries,[5-8] with one study in the United States.[9]A couple of studies found increased travel time to radiation increased one's risk for death.[5,6] Another study did not find increased travel impacting the risk of obtaining radiation and surgery, which in turn would impact survival.[10] This study offers new findings of increased travel time to various types of treatment (chemotherapy, surgery, and radiation) and to screening and their impact colon cancer mortality.

Comorbidities as a risk for colon cancer or CRC mortality have been examined with novel measures and had varying results regarding statistical significance.[1-4,11,12] These studies summed comorbidities or used various indices (Elixhauser, Charlson-Deyo, and Charlson comorbidity index). Studies using the Charlson comorbidity index (CCI) found an increase in index also increases one's risk for colon cancer or CRC mortality, but the results were nonsignificant.[2,13] This study adds to using CCI and these findings were statistically significant and demonstrated that an increase in the CCI also increases one's risk for colon cancer mortality.

Limitations

The limitations of this study are in regards to the Medicare population, comorbidity measure, race, travel time to treatment, and travel time to screening. This study cannot be generalized to the general public since it is a Medicare population with cancer. The Medicare population has different characteristics than the general population: more urban elderly, more affluent, and Medicare insurance coverage.

The comorbidity measure is potentially underestimated. Having an underestimation of comorbidities would create lower comorbidity scores. The underestimation of comorbidity scores may also give an underestimation of risk for colon cancer mortality.

The AI/AN sample is small, in comparison to the NHW population. Thus, the study did not have statistical significance for many of the risk factors that were examined. However, even though there was increased risk for the AI/AN race and it was not significant, it does suggest that there is potential increased risk for AI/AN. The lack of sample size for the AI/AN population is an issue and will continue to be an issue because of the exclusion of AI/AN from Arizona and Alaska from the SEER-Medicare database.

Treatment travel times may be underestimated for the AI/AN population living on reservations. Many reservations do not have street addresses and their location was determine by postal zip codes, which most likely will be nearer to a health provider providing treatment and screening procedures.

There may be also an underestimation of screening travel times. In order to determine a centroid within a screening provider's zip code area, centroids were determined using the addresses of treatment providers. This method would overestimate

screening providers and thus would increase screening facilities for all. This might be more problematic in less populated areas since the census tracts and zip code areas are larger in less populated areas.

Strengths

The strengths of this study are in regards to type of database, number of cases, claims data, type of data, and geographic locations. This SEER-Medicare database is a population database. Therefore, this database includes all the colon cancer patients with Medicare coverage. The database also includes a large number of cases, which is favorable for survival study. The data are also longitudinal from time of Medicare coverage until death; the data are rich in information over time. The database also has a diverse geographic area across the nation, including both urban and rural participants.

Conclusion

There are differences in risk factors for colon cancer survival between NHW and AI/AN. These differences need to be considered when taking survival improvements into consideration for each population. Comorbidities are also an issue for colon cancer patients and additional studies need to examine the mechanism(s) of how comorbidities influences poor survival.

Additional research includes examining the impact of comorbidities and travel times to screening and treatment impacts rectal cancer. Also, examining the density of treatment providers and determining if density of providers impacts survival is necessary. And, understanding the decision-making process of NHW and AI/AN and uncovering the influences participating (or not) in a colonoscopy and examining the data based on travel

times to screening facility is needed. A similar study is also needed in examining the decision process of chemotherapy treatment compliance. Screening is often encouraged to obtain early detection and thus, improving survival. And, it appears that NHW (and possibly AI/AN) living a distant away need assistant in obtaining screening. However, it appears that in the AI/AN population, uncovering factors influencing chemotherapy compliance might be the mechanism survival improvement.

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